Transforming primary care for anxiety disorders

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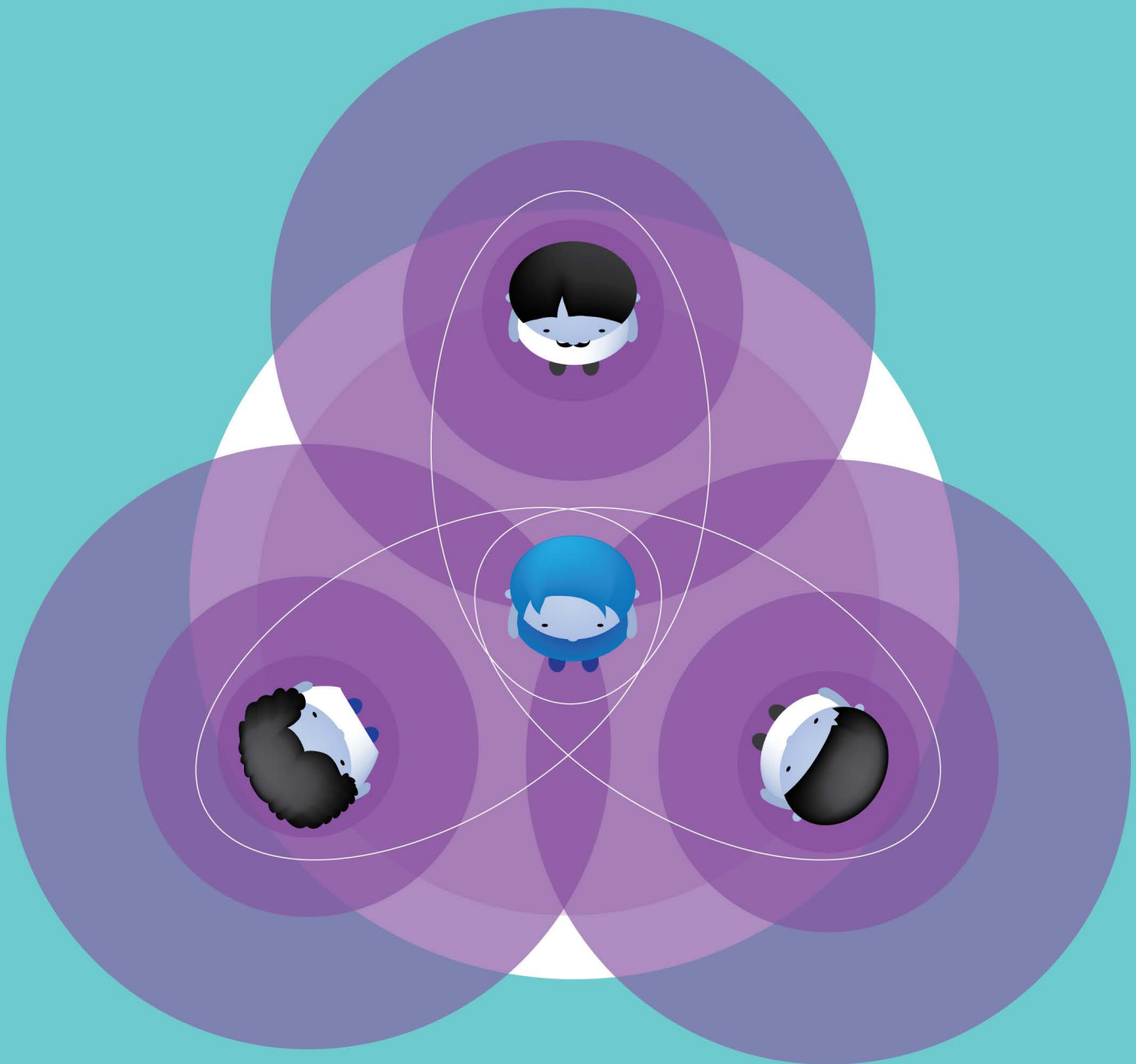
TRANSFORMING PRIMARY CARE FOR ANXIETY DISORDERS
THE COLLABORATIVE STEPPED CARE MODEL

Anna Muntingh



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Contents

Learn from yesterday, live for today, hope for tomorrow.
The important thing is not to stop questioning.

Albert Einstein (1879 – 1955)

Chapter 1

General introduction

Chronic illness: the largest problem in modern health care

Major advances in health care have led to the minimisation of infectious diseases in the 20th century. People tend to live longer and healthier lives, especially in the more developed countries. In the 21st century we have a new problem: worldwide around 50% of the disease burden is caused by non-communicable diseases which frequently run a chronic or recurrent course (WHO 2008). In high income countries, this type of diseases accounts for even 85% of the burden of disease (WHO 2008). In the Netherlands, there are around 4.5 million adults with such a chronic illness and expectations are that these numbers will accumulate in the near future (Gommer *et al.* 2010). Prevalent chronic illnesses are cardiovascular disease, diabetes and various mental disorders. Chronic illnesses are conditions that need "continuous adjustments by the affected person and interactions with the health care systems" (Improving chronic illness care & Group Health Research Institute 2012). The quality of care for chronic illnesses is often below the optimal standard. A review concluded that in the United States, adults with a chronic condition receive just over 50% of recommended care according to quality indicators (McGlynn *et al.* 2003). Care for chronic illnesses is complex and differs from care for acute diseases. While a reactive approach and one or more health care providers working independently is appropriate for acute diseases, chronic conditions need continuous and more proactive attention from both patients and providers. Common problems in care for patients with chronic conditions are the fragmented communication between health care providers involved, the absence of planned interactions and insufficient involvement of the patient in the care process (Wagner *et al.* 2001).

Improving care for chronic illnesses: the chronic care model

As a reaction to problems identified in chronic care, multifaceted strategies were developed to improve and integrate care. Those strategies were directed at improving knowledge of the provider or the patient about the chronic illness, or did address organisational changes such as adding a nurse specialist to a primary care practice team. A review about diabetes care (Renders *et al.* 2001) shed some light on the effectiveness of different strategies by indicating that strategies focussing on both the professional and the organisational system may improve diabetes *management*, while

adding patient education or a nurse care manager improve *patient outcomes*. This evidence led researchers to conclude that a model was needed that included various forms of interventions that could be used as a theoretical framework: the chronic care model (Wagner *et al.* 2001).

The chronic care model has six elements that should foster quality improvement: self-management support, decision support, delivery system design, clinical information systems, health care organisation, and community resources (see Table 1) (Bodenheimer *et al.* 2002).Effort directed at improvements on all of these levels, should result in enhanced self-management, efficient and high quality encounters between health care professionals and patients and improved patient outcomes (Bodenheimer *et al.* 2002).

The chronic care model was widely adopted, particularly in managed care settings, to improve the quality of care for different chronic illnesses and numerous studies have been performed evaluating its effectiveness. A recent review suggests that the model leads to quality improvements in most types of chronic care (Coleman *et al.* 2009). Due to the variation in the elaboration of the chronic care model, it is difficult to summarise results of the studies. There is no consensus yet about which elements are crucial for the effectiveness of the chronic care model (Vrijhoef 2010).

The use of the chronic care model in mental health care

At the same time of the development of the chronic care model, researchers in the field of depression made similar movements towards a different organisation of primary care. They found that interventions consisting of providing feedback about depression scores of patients did not lead to better outcomes for patients with depression (Katon & Gonzales 1994). A collaborative care model was developed which had many similarities with the chronic care model of Wagner and colleagues (Katon *et al.* 2001; Katon *et al.* 2010). The collaborative care model as evaluated in the early trials encompassed patient education materials, the use of allied health professionals (care managers) who provided monitoring and follow-up and sometimes provided evidence based psychotherapy, the use of a monitoring tool (PHQ-9), a liaised psychiatrist who provided consultations about antidepressant medication and

Table 1. Elements of the chronic care model

1. Self management support

- Emphasise the patient's central role.
- Use effective self-management support strategies that include assessment, goal-setting, action planning, problem-solving, and follow-up.
- Organise resources to provide support.

2. Decision support

- Embed evidence-based guidelines into daily clinical practice.
- Integrate specialist expertise and primary care.
- Use proven provider education methods.
- Share guidelines and information with patients.

3. Delivery system design

- Define roles and distribute tasks among team members.
- Use planned interactions to support evidence-based care.
- Provide clinical case management services for high risk patients.
- Ensure regular follow-up.
- Give care that patients understand and that fits their culture.

4. Clinical information systems

- Provide reminders for providers and patients.
- Identify relevant patient subpopulations for proactive care.
- Facilitate individual patient care planning.
- Share information with providers and patients.
- Monitor performance of team and system.

5. Health care organisations

- Visibly support improvement at all levels, starting with senior leaders.
- Promote effective improvement strategies aimed at comprehensive system change.
- Encourage open and systematic handling of problems.
- Provide incentives based on quality of care.
- Develop agreements for care coordination.

6. Community resources and policies

- Encourage patients to participate in effective programs.
- Form partnerships with community organisations to support or develop programs.
- Advocate for policies to improve care.

(Group Health's MacColl Insitute 2007)

supervised the caseload of care managers and the use of IT support to facilitate outcome monitoring and caseload supervision (Katon *et al.* 2010).
The rationale behind these collaborative care programs was that patient outcomes could be improved by 1) organising primary and secondary care practice differently (i.e. adding a care manager and consultant psychiatrist to the primary care team), 2) making treatment more systematic and pro-active and 3) enhancing patient self-management. Many randomised controlled trials were conducted and evidence accumulated rapidly that collaborative care was more effective than care as usual for primary care patients with depression in the United States (Gilbody *et al.* 2003). At present, over 60 trials considering collaborative care management for depression have been conducted, also in specific groups such as patients with depression and diabetes (Van der Feltz-Cornelis *et al.* 2010), teenagers or low-income patients (Gilbody *et al.* 2006; Thota *et al.* 2012). Two meta-analyses considering publications until 2004 (Gilbody *et al.* 2006) and from 2004 until 2009 (Thota *et al.* 2012) concluded that collaborative care leads to a significant improvement compared to care as usual for patients with depression, with a small to moderate clinical effect.

Expanding the evidence of collaborative care for mental disorders

Most research on collaborative care for mental disorders stems from managed health care settings in the United States. However, there are some important differences between primary care in the United States and in European countries which may influence the implementation and comparative effectiveness of collaborative care (de Jong *et al.* 2009). When we look at the primary care system in the Netherlands, for example, general practitioners receive a more extensive training in mental health care than general practitioners in the United States. Furthermore, accessibility of mental health services is generally lower for American citizens compared to Dutch citizens due to financial barriers (Russell 2010; Westert *et al.* 2010). Lastly, in the United States primary care practices usually employ a larger number of professionals than in the Netherlands (de Jong *et al.* 2009). For those reasons, it is important to test if collaborative care may also improve care in a system such as seen in the Netherlands. Furthermore, as research has focussed mainly on collaborative care for depression, additional evidence of its effectiveness for other mental disorders is needed.

Fortunately, research on collaborative care outside the United States and research focussing on mental disorders other than depression is emerging. A few collaborative care studies in primary care were conducted in the Netherlands. Van der Feltz-Cornelis and colleagues (2006) examined a collaborative care model involving psychiatric consultation in primary care for patients with medically unexplained symptoms and compared this to care as usual. They found that the collaborative care model resulted in better patient outcomes than care as usual (Van der Feltz-Cornelis *et al.* 2006). In a study of Van Orden and colleagues (2009) a collaborative care program for patients with diverse mental health problems was compared to referral to specialist mental health care. This study indicated that collaborative care was as effective as specialist mental health care and that patients in the collaborative care group needed fewer treatment sessions, had shorter waiting times, a shorter duration of treatment and generated lower health care costs (van Orden *et al.* 2009). In a recent study about collaborative care for depression it was shown that significantly more patients with major depression receiving collaborative care responded adequately to treatment than patients receiving usual primary care (Huijbregts *et al.* 2012).

Collaborative care for anxiety disorders

Research about collaborative care for anxiety disorders is scarce and almost inexistent outside the United States. Collaborative care does seem to be a promising method to improve care for anxiety disorders (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; Roy-Byrne et al. 2005a; Roy-Byrne *et al.* 2001). Anxiety disorders have many similarities with chronic somatic conditions and with depression (although there also differences such as potential avoidance behaviour that is typical for patients with anxiety disorders). First, most anxiety disorders are fairly chronic: around half of the patients with an anxiety disorder still suffers from the disorder 7 years later (Rhebergen *et al.* 2011). Second, as in care for chronic conditions, different (mental) health care professionals are involved in the treatment for anxiety disorders next to the general practitioner. Third, self-management, or learning to cope with anxiety is a very important aspect of reducing the impact of the anxiety on a patient's life (Oosterbaan & Verhaak 2012). Last, the quality of treatment for anxiety disorders is often below optimal standards, especially in primary care (Fernandez *et al.* 2007). The collaborative

care model might improve care, by integrating mental health expertise into primary care, ensuring evidence-based treatment, systematic monitoring and follow-up and supporting self-management of the patient.

Collaborative stepped care: the way forward for improving treatment of anxiety disorders?

In health care systems where expenditures are increasing rapidly and where there is a shortage of personnel, the efficiency of health care delivery is increasingly important. During the 1990's "doing more with less" became a popular statement (Davison 2000). In health care, this idea was translated into stepped care, which means that treatment is started with the least intrusive and expensive intervention possible and more intrusive and expensive interventions are only offered when the therapeutic goal is not reached (Davison 2000). Stepped care appeals to researchers and policy makers to create a more efficient mental health care system and was included in several clinical guidelines (Spijker *et al.* 2010; National Institute for Health and Clinical Excellence 2011). However, despite the evidence of the equal effectiveness of low-intensity treatments compared to high-intensity treatments (van Boeijen *et al.* 2005; Cuijpers *et al.* 2010), evidence for the relative effectiveness or efficiency of a complete stepped care program for mental health problems compared to usual primary care is limited and equivocal (Bower & Gilbody 2005; Richards 2012). For example, one randomised controlled trial found a positive effect of a stepped care program to prevent anxiety and depression in elderly individuals compared to care as usual (van't Veer-Tazelaar *et al.* 2009). A subsequent randomised controlled trial found no difference in treatment response between a stepped care program and care as usual in elderly individuals with depressive symptoms (van der Weele *et al.* 2012). Both trials were conducted in Dutch primary care. A recent randomised controlled trial conducted in the Netherlands found no evidence of improved patient outcomes when comparing a comprehensive stepped care program to usual primary care in adults with depressive or anxious symptoms (Seekles *et al.* 2011). The authors argue that a low need for treatment, a high chronicity of anxiety and depression and a low adherence to the guided self-help step might have influenced the minimal effectiveness of the stepped care treatment. They suggest that a stepped care approach embedded in a

collaborative care program might increase the effectiveness (Seekles *et al.* 2011). Collaborative care may indeed provide the adequate framework to provide stepped care. In collaborative care, patient adherence is encouraged by the use of a treatment plan and regular follow-up by the care manager. Furthermore, the structured collaboration between the general practitioner, care manager and psychiatrist may prevent a patient from dropping out of treatment and may contribute to a more flexible approach to the stepped care program when the first steps do not seem to be the adequate treatment for a particular patient. However, a collaborative stepped care model for anxiety disorders in primary care has not yet been evaluated.

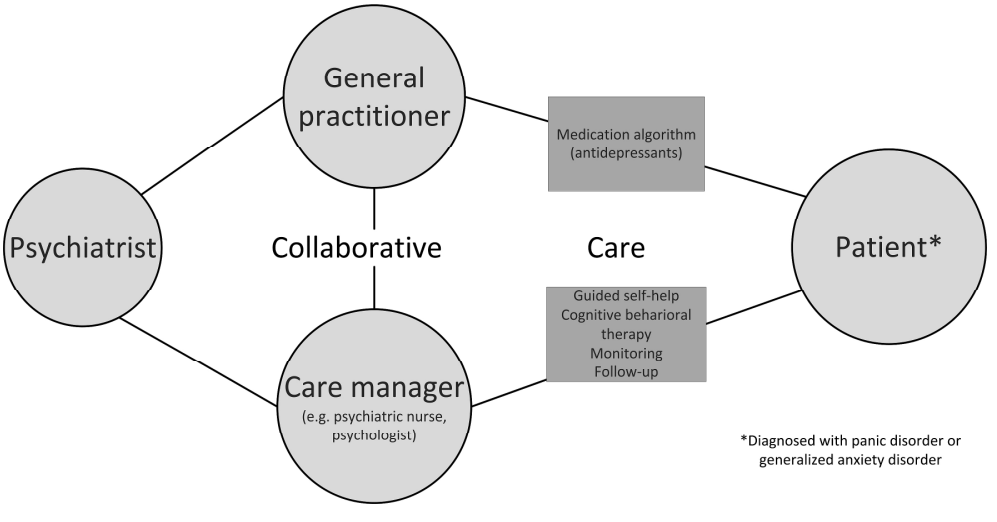

Figure 1. The collaborative care model for anxiety disorders
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Panic disorder and generalised anxiety disorder as target conditions for collaborative stepped care

Panic disorder and generalised anxiety disorder are two anxiety disorders for which the collaborative stepped care model may be suitable. Both disorders are prevalent in primary care and disabling, generally run a chronic course, produce high costs in health care and society and are often inadequately treated in primary care while evidence based, short duration treatments do exist. Social phobia is also a prevalent disorder in primary care, however, evidence based short duration protocols for treating this disorder in primary care are of limited availability (Seekles *et al.* 2012)

Prevalence and course of panic disorder and generalised anxiety disorder

Panic disorder is an anxiety disorder characterised by frequent unexpected panic attacks and a persistent fear of having these attacks (American Psychiatric Association 2001). A panic attack is a sudden increase in anxiety, accompanied by disturbing physical symptoms such as palpitations, nausea and dizziness. Often, people who experience panic attacks start avoiding activities or public places from which escaping might be difficult, such as travelling by train or going to a busy mall (agoraphobia). The 12 month prevalence of panic disorders is estimated at 1.5% in the general population (de Graaf *et al.* 2010) and 4% in primary care (Roy-Byrne *et al.* 2005b). Generalised anxiety disorder is characterised by excessive and uncontrollable worrying (American Psychiatric Association 2001). People with a generalised anxiety disorder anticipate negative life events to happen such as the loss of a loved one or financial bankruptcy. They also experience physical symptoms of sustained anxiety such as difficulty concentrating, muscle tensions and sleep problems. The prevalence of generalised anxiety disorder in the general population is estimated at 1.7% (de Graaf *et al.* 2010) and at 5.8% in primary care attendees (Roy-Byrne *et al.* 2005b). The course of a panic disorder and generalised anxiety disorder is chronic or intermittent. Although the majority (57%) of adults having a panic disorder reaches remission within two years, many of them still experience subclinical anxiety symptoms or a recurrence of panic attacks (Batelaan *et al.* 2010). Generalised anxiety disorder tends to have a more chronic course than panic disorder, with only 23% of adults with generalised anxiety disorder achieving remission within two years (Yonkers *et al.* 2003; Rhebergen *et al.*

2011). In conclusion, panic disorder and generalised anxiety disorder are prevalent and chronic conditions that need continuous attention of both the patient and health care providers.

Consequences of panic disorder and generalised anxiety disorder

Anxiety disorders rank third on the list of leading causes of the burden of disease in the Netherlands, accounting for 4.4% of the total burden of disease in the Netherlands (Gommer *et al.* 2010). Both panic disorder and generalised anxiety disorder lead to considerable disability (Bruffaerts *et al.* 2012), reduced quality of life (Olatunji *et al.* 2007) and absence from or reduced productivity at work (de Graaf *et al.* 2012). The negative impact of panic disorder and generalised anxiety disorder on quality of life and productivity is comparable to or even greater than seen in depression and chronic conditions such as arthritis or heart disease (Buist-Bouwman *et al.* 2006; Bruffaerts *et al.* 2012). Patients with panic disorder or generalised anxiety disorder generate considerable health care costs (Andlin-Sobocki & Wittchen 2005). For example, they visit the general practitioner more frequently (de Waal *et al.* 2008) and they make use of specialists more often than patients without a mental disorder (Roy-Byrne & Wagner 2004; Roy-Byrne *et al.* 2005b). Consequently, panic disorder and generalised anxiety disorder are not only a burden for patients and their relatives, but also for the health care system and the society as a whole.

Evidence-based treatment for panic disorder and generalised anxiety disorder

Several effective treatment methods for panic disorder and generalised anxiety disorder are available, of which the most well established are cognitive behavioural therapy and antidepressant medication (van Balkom *et al.* 1997; Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ 2010; National Institute for Health and Clinical Excellence 2011). Antidepressants are considered to sort their effect by altering the uptake of neurotransmitters in the brain. They must be taken daily, for at least six months (Bandelow *et al.* 2012). Cognitive behavioural therapy is a form of psychotherapy, teaching a patient with anxiety to recognise thoughts that lead to anxiety and how to modify these thoughts (Craske 2009). Another important element of cognitive behavioural therapy is exposure (Sanchez-Meca *et al.* 2010), which means

that people are encouraged to engage in situations they fear and they tend to avoid because of their anxiety. Most patients with panic disorder or generalised anxiety disorder receive care in primary care (Stein *et al.* 2011; Verhaak *et al.* 2012). However, while many patients with anxiety disorders receive some psychological support in primary care, a minority of patients receives adequate treatment with cognitive behavioural therapy or antidepressants in primary care (Young *et al.* 2001; Smolders *et al.* 2009; Stein *et al.* 2011).

Problems in treatment for panic disorder and generalised anxiety disorder

Several problems hamper the treatment of panic disorder and generalised anxiety disorder in current primary care. First of all, many patients with an anxiety disorder may not be recognised as having an anxiety disorder. Patients are hesitant to seek help for their anxiety problems for different reasons, such as wanting to solve the problem on their own (van Beljouw *et al.* 2010), avoidance of distress, or a low confidence in professional help (Prins *et al.* 2009). Patients often find it difficult to disclose their problems to a medical doctor (Kadam *et al.* 2001). When they do have an encounter with their general practitioner they tend to ask help for the physical symptoms accompanying the anxiety disorder, which makes it difficult for general practitioners to recognise and discuss the anxiety disorder (Tylee & Walters 2007). A second problem in primary care treatment for panic and generalised anxiety disorder, is that most patients are treated with antidepressants (Smolders *et al.* 2009; Stein *et al.* 2011), while the majority of patients prefers psychological treatment (Prins *et al.* 2009). This may have to do with the limited time available for general practitioners and the limited training they have had in providing cognitive behavioural therapy (Van Marwijk *et al.* 2004). Furthermore, patients are not always willing to be referred or to seek treatment from a mental health professional (Prins *et al.* 2009) and sometimes there are financial or practical barriers such as insurance coverage or waitlists that limit access to mental health care (Grembowski *et al.* 2002; Koopmans & Verhaak 2012). On the other hand, lengthy treatments in specialised mental health care are not always wanted or needed to treat patients effectively (van Boeijen *et al.* 2005). Hence, an increase in the provision of short duration, effective psychological treatments provided in the primary care setting may improve the quality of care (Richards 2012). However, few

professionals in primary care use short duration evidence based therapies, such as guided self-help (Zwaanswijk & Verhaak 2009). A different problem in primary care concerns the continuity of care. Because of the fragmented contacts between health care providers, information about the (ongoing) treatment of a patient is often inadequately transferred or shared (Muntingh *et al.* 2012). Furthermore, structural monitoring and follow-up to prevent a relapse of the disorder when treatment has been successfully concluded is uncommon in primary care (Muntingh *et al.* 2012).

Collaborative stepped care for panic disorder and generalised anxiety disorder: the solution to all problems encountered in primary care?

A collaborative stepped care model may be an effective and efficient method to tackle the problems mentioned above. In the collaborative stepped care model, a care manager, general practitioner and psychiatrist work together to provide high quality treatment in primary care, while avoiding unnecessary prescription of medication or referral to specialty mental health care. The care manager provides stepped care, short duration evidence based treatment in the primary care practice and ensures continuity of care by structurally monitoring the patient's symptoms. The general practitioner may use anxiety scales to assist in detecting and diagnosing anxiety disorders and makes use of an algorithm to effectively prescribe antidepressant medication. The psychiatrist is available to advise the care manager and general practitioner and adjust the treatment plan when necessary. The professionals share information about the ongoing treatment and the patient is actively involved in treatment to promote self-management and adherence to treatment. However, the effectiveness of collaborative stepped care for anxiety disorders has not been thoroughly studied yet. Therefore, the primary aim of this thesis is to evaluate the effectiveness of collaborative stepped care for panic disorder and generalised anxiety disorder in primary care. Furthermore, the costs of collaborative stepped care relative to its effectiveness is examined. Last, because correct recognition and diagnosis of the anxiety disorder is a prerequisite for the provision of collaborative stepped care, manners to improve recognition and assessment of anxiety disorders are studied.

Outline of this thesis

Chapter 2 aims to answer the question whether collaborative care for anxiety disorders in primary care is an effective intervention. The literature was systematically searched for randomised controlled trials reporting about the effectiveness of collaborative care for adults with anxiety disorders in primary care in reducing anxiety symptoms. Five randomised controlled trials were included and the results of these studies are statistically summarised.

Chapter 3 is comprised of two articles addressing the question whether collaborative stepped care for panic disorder and generalised anxiety disorder is more effective in reducing anxiety symptoms than care as usual. In the first article, the methods and design of a randomised controlled trial to evaluate this question are described. The design was a cluster randomised controlled trial in which half of the participating primary care professionals were trained to provide collaborative stepped care and half of the primary care professionals would provide care as usual. The second article describes the results of this cluster randomised controlled trial in which 43 primary care practices with 31 mental health professionals participated and 180 patients with panic disorder or generalised anxiety disorder were recruited. The reduction in anxiety symptoms of patients in the collaborative stepped care group (114 patients) and the care as usual group (66 patients) over the course of one year is compared. Furthermore, the actual care delivered to patients in both groups is described to provide insight into the working and the feasibility of the collaborative stepped care model.

Chapter 4 evaluates whether collaborative stepped care is cost-effective compared to care as usual. The medical costs of both interventions are calculated based on contacts with health care providers and medication costs. Subsequently these costs are related to the quality of life gained in both groups. A second analysis also takes costs into account that are related to the productivity of participants (i.e. sickness absence or reduced productivity at work).

Chapter 5 describes two studies that examine how recognition and assessment of anxiety disorders may be improved using a questionnaire. The first study investigates the added value of the Patient Health Questionnaire (PHQ) in detecting anxiety disorders in 170 primary care patients at risk for anxiety disorders and in 141 patients identified by their general practitioner as having a probable anxiety disorder. Patients were recruited within the cluster randomised controlled trial described in chapter 3. A second study assesses the ability of the Beck Anxiety Inventory (BAI) to measure the severity of anxiety symptoms in primary care patients with different anxiety disorders. Patients were recruited in a large cohort study (the Netherlands Study of Depression and Anxiety, NESDA). The mean scores of 1601 primary care patients with panic disorder with or without agoraphobia, generalised anxiety disorder, social phobia or agoraphobia and of patients with no disorder, a depressive disorder or multiple disorders are compared.

Finally, in **chapter 6** the main findings of this thesis and implications for research and practice are discussed.

REFERENCES

American Psychiatric Association (2001). *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV)*. American Psychiatric Publishing: Washington, DC.

Andlin-Sobocki, P. & Wittchen, H. U. (2005). Cost of anxiety disorders in Europe. *Eur J Neurol.* **12 Suppl 1**, 39-44.

Bandelow, B., Sher, L., Bunevicius, R., Hollander, E., Kasper, S., Zohar, J. & Moller, H. J. (2012). Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract* **16**, 77-84.

Batelaan, N. M., de Graaf, R., Penninx, B. W. J. H., Van Balkom, A. J. L. M., Vollebergh, W. A. M. & Beekman, A. T. F. (2010). The 2-year prognosis of panic episodes in the general population. *Journal of Affective Disorders* **121**.

Bodenheimer, T., Wagner, E. H. & Grumbach, K. (2002). Improving primary care for patients with chronic illness. *Jama* **288**, 1775-1779.

Bower, P. & Gilbody, S. (2005). Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry* **186**, 11-17.

Bruffaerts, R., Vilagut, G., Demyttenaere, K., Alonso, J., Alhamzawi, A., Andrade, L. H., Benjet, C., Bromet, E., Bunting, B., de, G. G., Florescu, S., Gureje, O., Haro, J. M., He, Y., Hinkov, H., Hu, C., Karam, E. G., Lepine, J. P., Levinson, D., Matschinger, H., Nakane, Y., Ormel, J., Posada-Villa, J., Scott, K. M., Varghese, M., Williams, D. R., Xavier, M. & Kessler, R. C. (2012). Role of common mental and physical disorders in partial disability around the world. *Br J Psychiatry*.

Buist-Bouwman, M. A., de Graaf, R., Vollebergh, W. A., Alonso, J., Bruffaerts, R. & Ormel, J. (2006). Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta psychiatrica Scandinavica* **113 (6)**, 492-500.

Coleman, K., Austin, B. T., Brach, C. & Wagner, E. H. (2009). Evidence on the Chronic Care Model in the new millennium. *Health Aff.(Millwood.)* **28**, 75-85.

Craske, M. (2009). *Cognitive-behavioral therapy*. American Psychological Association: Washington D.C.

Cuijpers, P., Donker, T., van Straten, A., Li, J. & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med* **40**, 1943-1957.

Davison, G. C. (2000). Stepped care: doing more with less? *Journal of Clinical Psychology* **68**, 580-585.

de Graaf, R., ten Have, M., & van Dorsselaer, S. (2010). De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: Opzet en eerste resultaten [Mental health in the Dutch general population. Design and results of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) In Dutch.].

de Graaf, R., Tuithof, M., van Dorsselaer, S. & ten Have, M. (2012). Comparing the effects on work performance of mental and physical disorders. *Soc Psychiatry Psychiatr Epidemiol*.

de Jong, S. J., van Steenbergen-Weijenburg, K. M., Huijbregts, K. M., Vlasveld, M., Marwijk, H. W. J., Beekman, A. & van der Feltz-Cornelis C.M. (2009). The depression

initiative. Description of a collaborative care model for depression and of the factors influencing its implementation in the primary care setting in the Netherlands. *International Journal of Integrated Care* **9**.

de Waal, M. W., Arnold, I. A., Eekhof, J. A., Assendelft, W. J. & Van Hemert, A. M. (2008). Follow-up study on health care use of patients with somatoform, anxiety and depressive disorders in primary care. *BMC Fam Pract* **9**.

Fernandez, A., Haro, J. M., Martinez-Alonso, M., Demyttenaere, K., Brugha, T. S., Autonell, J., De Girolamo, G., Bernert, S., Lepine, J. P. & Alonso, J. (2007). Treatment adequacy for anxiety and depressive disorders in six European countries. *Br J Psychiatry* **190**, 172-173.

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch.Intern.Med.* **166**, 2314-2321.

Gilbody, S., Whitty, P., Grimshaw, J. & Thomas, R. (2003). Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *Jama* **289**, 3145-3151.

Gommer, A. M., Hoeymans, N., & Poos, M. J. J. C. (2010). Wat is de ziektelast in Nederland? In: Volksgezondheid Toekomstverkenning, Nationaal Kompas Volksgezondheid. RIVM: Bilthoven.

Grembowski, D. E., Martin, D., Patrick, D. L., Diehr, P., Katon, W., Williams, B., Engelberg, R., Novak, L., Dickstein, D., Deyo, R. & Goldberg, H. I. (2002). Managed care, access to mental health specialists, and outcomes among primary care patients with depressive symptoms. *J Gen Intern Med* **17**, 258-269.

Group Health's MacColl Insitute. Does the chronic care model work? http://www.improvingchroniccare.org/index.php?p='Tackling_the_Chronic_Care_Crisis'_CD&s=172 Last visited June 27th 2012.

Huijbregts, K. M., de Jong, F. J., Van Marwijk, H. W. J., Beekman, A. T. F., Adèr, H., Hakkaart-Van Roijen, L., Unutzer, J. & Van der Feltz-Cornelis C.M. (2012). A target-driven Collaborative Care model for Major Depressive Disorder is effective in primary care in the Netherlands. A Randomized Clinical Trial from the Depression Initiative. *Journal of Affective Disorders,* accepted for publication.

Improving chronic illness care & Group Health Research Institute. The chronic care model. http://www.improvingchroniccare.org/index.php?p='The_Chronic_Care_Model&s=2 Last visited June 27th 2012.

Kadam, U. T., Croft, P., McLeod, J. & Hutchinson, M. (2001). A qualitative study of patients' views on anxiety and depression. *Br J Gen Pract* **51**, 375-380.

Katon, W., Unutzer, J., Wells, K. & Jones, L. (2010). Collaborative depression care: history, evolution and ways to enhance dissemination and sustainability. *Gen.Hosp.Psychiatry* **32**, 456-464.

Katon, W., Von, K. M., Lin, E. & Simon, G. (2001). Rethinking practitioner roles in chronic illness: the specialist, primary care physician, and the practice nurse. *Gen.Hosp.Psychiatry* **23**, 138-144.

Katon, W. J. & Gonzales, J. (1994). A review of randomized trials of psychiatric consultation-liaison studies in primary care. *Psychosomatics* **35**, 268-278.

Koopmans, B. & Verhaak, P. (2012). Verwacht zorggebruik als gevolg van de eigen bijdrage in de tweedelijns GGZ [Expected health care use as a result of a financial fee for the use of specialty mental health care. In Dutch] NIVEL, Utrecht.

Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ (2010). Multidisciplinaire Richtlijn Angststoornissen (tweede revisie). [Multidisciplinary guideline for anxiety disorders (second revision). In Dutch].

McGlynn, E. A., Asch, S. M., Adams, J., Keesey, J., Hicks, J., DeCristofaro, A. & Kerr, E. A. (2003). The quality of health care delivered to adults in the United States. *N Engl J Med* **348**, 2635-2645.

Muntingh, A. D. T., Hermens, M., Franx, G., Van Splunteren, P., & Nuyen, J. (2012). Hoe verhouden de werkelijke en wenselijke eerstelijns depressiezorg zich tot elkaar? Resultaten van een verkennend onderzoek in de huisartspraktijk. *[How does the actual depression care relate to optimal depression care? Results of an exploratory study in Dutch primary care. In Dutch]* In: *Trendrapportage GGZ. Deel 3: Kwaliteit en effectiviteit.* (ed. J. Nuijen). Trimbos-instituut: Utrecht.

National Institute for Health and Clinical Excellence 2011, Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. NICE clinical guideline 113.

Olatunji, B. O., Cisler, J. M. & Tolin, D. F. (2007). Quality of life in the anxiety disorders: a meta-analytic review. *Clin Psychol Rev* **27**, 572-581.

Oosterbaan, D. & Verhaak, P. (2012). Living with an anxiety disorder [Leven met een angststoornis, in Dutch]. In *Handboek Angststoornissen* (eds. A. J. L. M. Van Balkom, D. Oosterbaan, S. Visser and I. M. van Vliet). De Tijdstroom: Utrecht.

Prins, M. A., Verhaak, P. F., Van der Meer, K., Penninx, B. W. & Bensing, J. M. (2009). Primary care patients with anxiety and depression: need for care from the patient's perspective. *J Affect Disord* **119**, 163-171.

Renders, C. M., Valk, G. D., Griffin, S., Wagner, E. H., Eijk, J. T. & Assendelft, W. J. (2001). Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *Cochrane database of systematic reviews (Online)*, CD001481.

Rhebergen, D., Batelaan, N. M., de Graaf, R., Nolen, W. A., Spijker, J., Beekman, A. T. F. & Penninx, B. W. J. H. (2011). The 7-year course of depression and anxiety in the general population. *Acta Psychiatr Scand* **123**, 297-306.

Richards, D. A. (2012). Stepped care: a method to deliver increased access to psychological therapies. *Can J Psychiatry* **57**, 210-215.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005a). A randomized effectiveness trial of cognitive-

behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.

Roy-Byrne, P. P., Wagner, A. W. & Schraufnagel, T. J. (2005b). Understanding and treating panic disorder in the primary care setting. *Journal of Clinical Psychiatry* **66 Suppl 4**, 16-22.

Roy-Byrne, P. P. & Wagner, A. (2004). Primary care perspectives on generalized anxiety disorder. *J Clin Psychiatry* **65 Suppl 13**, 20-26.

Roy-Byrne, P. P., Katon, W., Cowley, D. S. & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* **58**, 869-876.

Russell, L. (2010). Mental health care services in primary care. Tackling the issues in the context of health care reform., Center for American Progress, Washington DC.

Sanchez-Meca, J., Rosa-Alcazar, A. I., Marin-Martinez, F. & Gomez-Conesa, A. (2010). Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. *Clin Psychol Rev* **30**, 37-50.

Seekles, W., Cuijpers, P., Kok, R., Beekman, A., van, M. H. & van, S. A. (2012). Psychological treatment of anxiety in primary care: a meta-analysis. *Psychol Med*, 1-11.

Seekles, W., van Straten, A., Beekman, A., van Marwijk, H. & Cuijpers, P. (2011). Stepped care treatment for depression and anxiety in primary care. a randomized controlled trial. *Trials* **12**, 171.

Smolders, M., Laurant, M., Verhaak, P., Prins, M., van, M. H., Penninx, B., Wensing, M. & Grol, R. (2009). Adherence to evidence-based guidelines for depression and anxiety disorders is associated with recording of the diagnosis. *Gen Hosp Psychiatry* **31**, 460-469.

Spijker, J., van Vliet, I. M., Meeuwissen, J. A. C. & Van Balkom, A. J. L. M. (2010). [Update of the multidisciplinary guidelines for anxiety and depression]. *Tijdschr Psychiatr* **52**, 715-718.

Stein, M. B., Roy-Byrne, P. P., Craske, M. G., Campbell-Sills, L., Lang, A. J., Golinelli, D., Rose, R. D., Bystritsky, A., Sullivan, G. & Sherbourne, C. D. (2011). Quality of and patient satisfaction with primary health care for anxiety disorders. *J Clin Psychiatry* **72**, 970-976.

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease, D. E., Jr. & Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med* **42**, 525-538.

Tylee, A. & Walters, P. (2007). Underrecognition of anxiety and mood disorders in primary care: why does the problem exist and what can be done? *J Clin Psychiatry* **68 Suppl 2**, 27-30.

van Balkom, A. J., Bakker, A., Spinhoven, P., Blaauw, B. M., Smeenk, S. & Ruesink, B. (1997). A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *J Nerv.Ment.Dis* **185**, 510-516.

van Beljouw, I., Verhaak, P., Prins, M., Cuijpers, P., Penninx, B. & Bensing, J. (2010). Reasons and determinants for not receiving treatment for common mental disorders. *Psychiatr Serv* **61**, 250-257.

van Boeijen, C. A., van Oppen, P., van Balkom, A. J., Visser, S., Kempe, P. T., Blankenstein, N. & van Dyck, R. (2005). Treatment of anxiety disorders in primary care practice: a randomised controlled trial. *Br J Gen Pract.* **55**, 763-769.

van der Feltz-Cornelis, C. M., Nuyen, J., Stoop, C., Chan, J., Jacobson, A. M., Katon, W., Snoek, F. J. & Sartorius, N. (2010). Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Science Direct* **General Hospital Psychiatry**, 380-395.

van der Feltz-Cornelis, C. M., van Oppen, P., Adèr, H. & van Dyck, R. (2006). Randomised Controlled Trial of a Collaborative Care Model with Psychiatric Consultation for Persistent Medically Unexplained Symptoms in General Practice. *Psychother.Psychosom.* **75**, 282-289.

van der Weele, G. M., de Waal, M. W. M., van den Hout, W. B., de Craen, A. J. M., Spinhoven, P., Stijnen, T., Assendelft, W. J. J., van der Mast, R. C. & Gussekloo, J. (2012). Effects of a stepped-care intervention programme among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomised controlled trial. *Age and ageing* **41**, 482-488.

van Marwijk, H. (2004). How to improve mental health competency in general practice training?--a SWOT analysis. *Eur J Gen Pract* **10**, 61-65.

van Orden, M., Hoffman, T., Haffmans, J., Spinhoven, P. & Hoencamp, E. (2009). Collaborative mental health care versus care as usual in a primary care setting: a randomized controlled trial. *Psychiatr Serv* **60**, 74-79.

van't Veer-Tazelaar, P. J., van Marwijk, H. W., van Oppen, P., van Hout, H. P., van der Horst, H. E., Cuijpers, P., Smit, F. & Beekman, A. T. (2009). Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Archives Of General Psychiatry, 2009 Mar; Vol.66 (3), pp.297-304.*

Verhaak, P. F. M., van Dijk, C. E., Nuijen, J., Verheij, R. A. & Schellevis, F. G. (2012). Mental health care as delivered by Dutch general practitioners between 2004 and 2008. *Scandinavian Journal of Primary Health Care.*

Vrijhoef, H. J. M. (2010). The future is to chronically ill [Chronisch zieken hebben de toekomst. Inaugurele rede. In Dutch].

Wagner, E. H., Austin, B. T., Davis, C., Hindmarsh, M., Schaefer, J. & Bonomi, A. (2001). Improving chronic illness care: translating evidence into action. *Health Aff.(Millwood.)* **20**, 64-78.

Westert, G. P., van den Berg, M. J., Zwakhals, S. L. N., de Jong, J. D., & Verkleij, H. (2010). *Dutch Health Care Performance Report 2010*, National Institute for Public Health and the Environment, Bilthoven.

WHO (2008). The global burden of disease (2004 update), World Health Organization.

Yonkers, K. A., Bruce, S. E., Dyck, I. R. & Keller, M. B. (2003). Chronicity, relapse, and illness--course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress.Anxiety* **17**, 173-179.

Young, A. S., Klap, R., Sherbourne, C. D. & Wells, K. B. (2001). The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry* **58**, 55-61.

Zwaanswijk, M. & Verhaak, P. F. M. (2009). Effectieve kortdurende interventies voor psychische problemen. Kennissynthese over hun toepasbaarheid in de huisartsenvoorziening. [Effective short duration interventions for psychological problems. Review of their applicability in Dutch primary care. In Dutch], NIVEL, Utrecht.

Chapter 2

Collaborative care interventions for anxiety disorders in primary care: a systematic review and meta-analysis

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Abstract

Background The effectiveness of collaborative care interventions targeting patient, provider and system changes have not been statistically summarised for patients with anxiety disorders.

Data sources A comprehensive literature search for published articles was performed using PubMed, Psycinfo, Embase, Cinahl and Cochrane library.

Study eligibility criteria Randomised controlled trials examining the effects of collaborative care for adult primary care patients with an anxiety disorder, compared to care as usual or another intervention were included.

Study appraisal and synthesis methods The selection of studies and risk of bias assessment were performed by two independent reviewers. The standardised mean difference on an anxiety scale closest to twelve months follow up was calculated and summarised using a random effects meta-analysis.

Results Of the 2556 studies found, five studies were included that all compared collaborative care to care as usual. The studies included a total of 1931 participants and varied in risk of bias. Collaborative care was superior to care as usual (ES = 0.27 95% CI 0.01-0.67). For patients with panic disorder (four studies), the effect size was moderate (ES = 0.44, 95% CI 0.30-0.59).

Conclusion Collaborative care seems to be a promising strategy for improving primary care for anxiety disorders. However, the number of studies is small and research almost exclusively originates from the United States.

1. Introduction

1.1 Background

Anxiety disorders constitute the most prevalent category of psychiatric disorders (Kessler *et al.* 2010). Anxiety disorders have a negative impact on quality of life and are associated with significant health care and productivity costs (Lepine 2002). Most anxiety disorders run a chronic or intermittent course (Yonkers *et al.* 2003), thereby causing sustained disability. Adults with an anxiety disorder mainly receive care in primary care (Young *et al.* 2001; Wang *et al.* 2005; Kessler *et al.* 2005). In many countries however, the quality of care for adults with anxiety disorders leaves room for improvement (Young *et al.* 2001; Fernandez *et al.* 2007). Although clinical guidelines recommend cognitive behavioural therapy or antidepressant medication as the treatment of choice in primary care, these evidence based treatments are not often adequately applied in primary care (Stein *et al.* 2011). Several barriers exist in providing evidence based care for anxiety disorders in primary care, which may be related to patient characteristics, provider characteristics or the organisational context of primary care (Nutting *et al.* 2002; Roy-Byrne *et al.* 2005a; Smolders *et al.* 2010). Diagnosing an anxiety disorder in primary care is difficult, because anxiety disorders are often accompanied by physical symptoms, social problems or depressive symptoms (Kessler *et al.* 2005; Kroenke *et al.* 2007). Moreover, patients are often hesitant to seek help for their anxiety problems (Prins *et al.* 2008; van Beljouw *et al.* 2010). Once a diagnosis has been made, there are other problems that form a barrier for effective treatment. On the level of the patient, low adherence to pharmacotherapy or psychotherapy is a frequently seen problem (van Geffen *et al.* 2009; Taylor *et al.* 2012). For primary care physicians it is often difficult to treat anxiety disorders as they may not have the necessary time and skills to provide cognitive behavioural therapy (Van Marwijk, 2004). The health care system contains barriers such as limited accessibility of mental health services (Grembowski *et al.* 2002; Richards 2012) and an organisation of care based on reactive interactions with patients, while this may not be the right approach for patients with chronic or fluctuating conditions such as anxiety disorders (Wagner *et al.* 2001). Historically, efforts for improving the quality of care have been directed at the education of health care providers. However, training of physicians

alone does not seem to lead to a significant improvement of the quality of care (Gilbody *et al.* 2003). Therefore, multifaceted interventions that focus on patient, provider and organisation of care have been proposed as the most promising strategy to improve primary mental health care (Gilbody *et al.* 2003; Heideman *et al.* 2005).
Collaborative or integrative care models are such multifaceted interventions aimed at improving the quality and organisation of primary mental health care. These models bring mental health expertise into primary care by introducing new members into the primary care team. Typically, this new member is a "care manager" with a background in mental health, who coordinates care, provides evidence based interventions and actively monitors the patient's symptoms (Katon *et al.* 2001). The care manager works in close collaboration with the primary care physician and both providers have access to the tailored advice of a psychiatrist. Although collaborative care models vary in the professionals involved, type of interventions used, the intensity of treatment and follow-up, a few essential elements have been described. These elements consist of cooperation between the primary care physician and at least one other professional, provision of evidence based treatment and active monitoring of symptoms and follow-up (Gilbody, Bower, Fletcher, Richards, and Sutton, 2006; Katon *et al.* 1995; van Steenbergen-Weijenburg *et al.* 2010). Interventions or organisational models similar to collaborative care are sometimes referred to as integrated care, enhanced care or care management.
The core feature of collaborative care is the collaboration of the primary care physician with a mental health care provider. In some collaborative care models, the primary care physician is only supported by a psychiatrist. In other collaborative care models, a nurse care manager is introduced in the primary care team who is supervised by a psychiatrist. The addition of a care manager to the primary care team is an interesting opportunity, because a (nurse) care manager is more accessible than a psychiatrist and can be trained to provide psychological interventions in the primary care setting. However, the organisation of care becomes increasingly difficult if more professionals are involved and the direct involvement of a psychiatrist might also have an advantage. Therefore, it may be interesting to know if the effects of collaborative care models including a care manager and a consultant psychiatrist differ from the effects of collaborative care models that include a consultant psychiatrist alone.

1.2 Rationale

Evidence of the effectiveness of collaborative care in the treatment of depression is well established and was reviewed thoroughly in two meta-analyses including 37 studies (Gilbody *et al.* 2006; Bower *et al.* 2006), demonstrating an overall benefit of collaborative care interventions over care as usual, with a small but robust clinical effect (d=0.25). A recent meta-analysis expanded this evidence reviewing 32 studies published during or after 2004, with a pooled effect size of 0.34 (Thota *et al.* 2012). Although anxiety disorders are just as prevalent and disabling as depression and may even be more chronic conditions (Rhebergen *et al.* 2011), studies about collaborative care for anxiety disorders have been scarce (Smolders *et al.* 2008). In a review of Smolders and colleagues (2008) only 3 collaborative care studies were included and results were not statistically summarised. Recent reviews about psychotherapies in primary care did exclude studies about collaborative care for anxiety disorders (Cape *et al.* 2010; Wampold *et al.* 2011; Seekles *et al.* 2012). Therefore, a systematic review and meta-analysis is needed to summarise results from (cluster) randomised controlled trials about the effectiveness of collaborative care for anxiety disorders in adult primary care patients. Furthermore, the effects of components of collaborative care relevant for its effectiveness in the treatment of anxiety disorders have not yet been studied.

1.3 Objectives

To examine to what extent collaborative care interventions reduce anxiety symptoms in primary care patients with an anxiety disorder versus a control condition or another active intervention, we performed a systematic review and meta-analysis of randomised, controlled trials. In addition, we evaluated the effects for specific anxiety disorders and the influence of the inclusion of a care manager in the collaborative care model.

2. Methods

2.1 Eligibility criteria

In this systematic review, randomised controlled trials (RCTs) were included that evaluated collaborative care compared to care as usual or another active intervention in adult primary care patients with an anxiety disorder and that reported outcomes on a standardised scale for anxiety severity.

2.1.1 Design

We included RCTs that randomised between patients (individual randomisation) or between primary care practices (cluster randomisation).

2.1.2 Participants

Studies had to include adult (>18 years) subjects recruited in a primary care setting with an anxiety disorder as established with a valid diagnostic interview, according to research diagnostic criteria or with a cut-off score on a validated scale. Comorbid medical or psychiatric conditions were allowed, as long as the intervention focused on the anxiety disorder.

2.1.3 Intervention

Collaborative care interventions were defined by the application of at least two out of the three following criteria (Von Korff *et al.* 1997; Gilbody *et al.* 2006; Bower *et al.* 2006; van Steenbergen-Weijenburg *et al.* 2010):

1. The primary care physician is supported by at least one other professional with a different field of expertise (e.g. care manager, consultant psychiatrist) and they work together in providing care for the patient.
2. Evidence-based treatment is provided.
3. Process and outcome of treatment is being monitored.

Studies evaluating the provision of services by an on-site mental health professional were excluded, unless reference was made to enhanced collaboration between the primary care physician and the mental health professional.

2.1.4 Comparison intervention

The collaborative care intervention could be compared to care as usual, a waitlist condition or another active intervention.

2.1.5 Outcomes

Studies that reported outcomes on a validated anxiety scale or interview were included. Standardised scales or interviews could measure general anxiety (across anxiety disorders) or measure a specific type of anxiety (e.g. panic disorder severity).

2.2 Information sources and search

We searched several medical and psychological databases from inception to May 14th 2012 without language restriction (Psycinfo, PubMed (Medline), Embase, The Cochrane Central Register of Controlled Trials and Cinahl). The highly sensitive search was performed by one author (AM) and an experienced librarian, using terms related to anxiety, primary care and randomised controlled trials. Both MeSH terms and free text words were used. See Box 1 for the full search strategy as performed in PubMed. The search in PubMed was adapted for use in the other databases. The reference lists of selected randomised controlled trials (RCTs) and reviews were checked for potentially relevant titles. The search was limited to published studies.

2.3 Study selection

Titles and abstracts of retrieved studies were screened independently by two reviewers (AM/CFC) using a list of inclusion criteria. If a study appeared eligible (or if eligibility was doubtful), the full text of an article was retrieved. All full text articles were assessed for eligibility by two independent reviewers (AM and AvB/HvM/CFC). Disagreement was resolved by consensus or eventually by a third reviewer.

2.4 Data collection process

The outcome data were extracted by two reviewers independently (AM and CFC). Other relevant characteristics of studies were extracted by one author (AM) using a form based on Cochrane criteria (Higgins & Deeks 2011) (see Table 1).

Box 1: PubMed Search History

Search	Most Recent Queries	Time	Result
#12	Search **#9 OR #10 OR #11**	08:53:48	955
#11	Search **#7** Limits: **Systematic Reviews**	08:49:18	196
#10	Search **#7** Limits: **Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial**	08:49:04	727
#9	Search **(#7 AND #8) NOT medline[sb]**	08:48:29	111
#8	Search **randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR comparative study [pt] OR evaluation studies [pt] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "placebos"[MeSH Terms] OR "research design"[MeSH Terms:noexp] OR "follow-up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms] OR "drug therapy"[Subheading] OR "clinical trial" [tw] OR "latin square" [tw] OR placebo* [tw] OR random* [tw] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw] OR trial[tiab] OR groups[tiab] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))**	08:48:11	6213954
#7	Search **#3 AND #6**	08:47:36	4922
#6	Search **#4 OR #5**	08:47:24	185546
#5	Search **"Primary Health Care"[Mesh] OR "primary care"[tiab]**	08:47:11	91683
#4	Search **("Family Practice"[Mesh] OR "Physicians, Family"[Mesh]) OR "family practice"[tiab] OR "general practice"[tiab] OR"family practices"[tiab] OR "general practices"[tiab] OR "family practitioner "[tiab] OR "general practitioner"[tiab] OR "family practitioners "[tiab] OR "general practitioners"[tiab] OR family medicine[tiab] OR "Physician Assistants"[Mesh] OR "Physician Assistant"[tiab] OR "Physician Assistants"[tiab] OR "Nurse Practitioners"[Mesh] OR "Nurse Practitioner"[tiab] OR "Nurse Practitioners"[tiab]**	08:46:55	115493
#3	Search **#1 OR #2**	08:46:08	149816
#2	Search **Anxiety[tiab] OR Anxieties[tiab] OR anxious[tiab] OR Nervousness[tiab] OR Agoraphobia*[tiab] OR Obsessive-Compulsive[tiab] OR Panic*[tiab] OR Phobia*[tiab] OR Phobic*[tiab] OR Claustrophobi*[tiab] OR (Stress[tiab] AND trauma*[tiab]) OR (Stress[tiab] AND posttrauma*[tiab])**	08:45:59	118672
#1	Search **"Anxiety"[Mesh:noexp] OR "Anxiety Disorders"[Mesh]**	08:45:16	92083

http://www.ncbi.nlm.nih.gov/pubmed/advanced - #

2.5 Data items

We extracted the mean and standard deviation of the intervention group and control group on anxiety scales at baseline and follow-up. Outcomes for anxiety disorders in general as well as outcomes for specific anxiety disorders were extracted. For studies using more than one validated anxiety scale as an outcome measure, we chose the scale that was most frequently reported in the other studies. If the mean and standard deviation were not reported, we searched for other data to calculate the effect size, such as a difference score with a standard deviation or confidence limits and p-value. Furthermore, data relevant for the interpretation of the findings were collected: design of the study, recruitment method, procedure used to diagnose the anxiety disorder, setting, sample size, details of the collaborative care intervention and the comparison intervention, anxiety scale used, follow-up measurements and outcomes. Details of the collaborative care intervention included the professionals involved (primary care physician, psychiatrist, care manager), interventions used, the number of sessions or consultations, the use of educational materials, the provision of monitoring and follow-up and the form of communication between professionals. For the comparison interventions we collected data about medication use and the use of mental health care services. Where published protocols of the studies included were available, they were used to supplement data about intervention details.

2.6 Risk of bias in individual studies

The risk of bias of each included study was assessed using a standard form based on Cochrane criteria (Higgins *et al.* 2011) by two reviewers (AM and AvB/HvM) independently. The form systematically enquired about possible sources of bias in randomised controlled trial, such as the adequacy of the randomisation procedure, allocation concealment, handling of missing data and selective reporting. Disagreement between reviewers about assessment ratings were resolved by consensus or a third reviewer (CFC).

2.7 Summary measures and synthesis of results

We statistically summarised the effectiveness of collaborative care interventions versus the comparison interventions using meta-analysis. The analyses were conducted using

the software package Comprehensive Meta Analysis version 2.0 (Borenstein *et al.* 2005). We calculated a standardised effect size (Cohens D (Cohen 1988)) from reported differences in means on a continuous anxiety scale between interventions at 12 months follow-up to using the computer program Comprehensive Meta-Analysis. Preferably, means and standard deviations were used to calculate the effect size *d*. However, when these data were not available, other reported data such as the difference in means and p-value were used or the standard deviation was calculated from the confidence interval as described in the Cochrane Handbook (Higgins & Deeks 2011). We summarised the standardised effect sizes using the random effects model, because we made the assumption that not all collaborative care interventions are inherently the same, resulting in a true variation in effect size between studies (Borenstein *et al.* 2009). High resolution plots were created to present the results.

2.8 Assessment of heterogeneity and risk of bias across studies

To assess the heterogeneity among studies we calculated the I^2 statistic which reflects the proportion of total variation across studies that is attributable to heterogeneity rather than chance. An I^2 of 0% means that there is no observed heterogeneity, while an I^2 of 25%, 50% and 75% may be interpreted as low, medium and high heterogeneity respectively (Higgins *et al.* 2003). Funnel plots were created and Duval and Tweedie's trim and fill method was used to examine the possibility of publication bias (Duval & Tweedie 2000). This method gives an estimate of the effect size after correcting for possible publication bias.

2.9 Additional analyses

A pre-envisioned subgroup analysis was performed to assess the effectiveness of collaborative care for patients with a specific anxiety disorder. In this analysis, a disorder-specific outcome measure (when available) was used to calculate the effect size. Furthermore, we assessed the influence of the inclusion of a care manager in the collaborative care model on the effect size of studies. Therefore, we performed a meta-regression in which the effects of collaborative care interventions with both a care manager and a consultant psychiatrist were compared to those of collaborative care interventions with only a consultant psychiatrist.

3. Results

3.1 Study selection

The literature search resulted in a total of 4035 retrieved citations. In addition, we examined references of 9 reviews and all the references of the retrieved studies, which resulted in 40 extra possibly relevant titles. After removal of duplicates, 2556 abstracts were available (see Figure 1). For 18 studies the full text paper was retrieved and examined for inclusion. After the exclusion of 13 studies (9 no collaborative care; 3 no separate outcome reported for patients with anxiety disorders; 1 report of other study) there were 5 studies that met all the inclusion criteria.

3.2 Characteristics of included studies

Five studies involving 1931 subjects (996 in the collaborative care condition, 935 in the control condition) were included in the review and the subsequent meta-analysis. Table 1 shows an overview of characteristics of the included studies.

3.2.1 Design

Four studies were individually randomised controlled trials (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; Roy-Byrne *et al.* 2005b, Roy-Byrne *et al.* 2001); one study used cluster randomisation on the level of primary care practices (König *et al.* 2009). The number of participants in each study ranged from 115 to 1004. Four of the studies were conducted in the United States (Rollman *et al.*2005; Roy-Byrne *et al.* 2010; 2005b; 2001); one study took place in Germany (König *et al.* 2009).

3.2.2 Participants

Two studies included only patients with panic disorder (Roy-Byrne *et al.* 2005b; 2001). One study (Rollman *et al.* 2005) included patients with panic disorder and/or generalised anxiety disorder and one study (Roy-Byrne *et al.* 2010) included patients with panic disorder generalised anxiety disorder, social phobia and posttraumatic stress disorder. These four studies used a structured interview to classify the anxiety disorder (CIDI, PRIME-MD). One study (König *et al.* 2009) focused on anxiety in general, determined by a cut-off score on the Patient Health Questionnaire. Two

studies used screening to recruit participants (Rollman *et al.* 2005; König *et al.* 2009), one study used referral of primary care physicians as recruitment method (Roy-Byrne *et al.* 2010) and two studies used both methods to recruit participants (Roy-Byrne *et al.* 2005b; 2001).

3.2.3 Collaborative care interventions

The elaboration of the collaborative care model varied considerably between studies. In all studies, a primary care physician and a psychiatrist were involved, while in three studies a care manager was introduced as well (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; 2005b). The care managers had different backgrounds, being master-level or doctoral-level behavioural health specialists (Roy-Byrne *et al.* 2005b), non-behavioural health specialists (Rollman *et al.* 2005) or clinical anxiety specialists (variety of registered nurses, social workers and psychologists, Roy-Byrne *et al.* 2010). All studies used evidence-based interventions, consisting of antidepressant medication and/or cognitive behavioural therapy. In one study (Roy-Byrne *et al.* 2001) the intervention consisted of psycho-education and medication management, in the other studies a form of CBT (guided self-help or face to face) was also offered. In four studies (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; 2005b; 2001) systematic follow-up by the care manager or the consultant psychiatrist was part of the collaborative care intervention and in two studies anxiety symptoms were monitored by the care manager with an anxiety scale (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010). Studies varied in what they reported about actual care that was delivered (see Table 2). All but one study (König *et al.* 2009) reported medication use and the number of contacts patients had with the care manager or psychiatrist during follow-up. Two studies (König *et al.* 2009; Rollman *et al.* 2005) reported the percentage of patients that had contact with a mental health professional (other than the care manager/psychiatrist). The study of König and colleagues (2009) did not report how many patients received the intended intervention (CBT by the primary care physician).

3.2.4 Comparison interventions

All studies compared the collaborative care intervention to care as usual by the primary care physician and did provide information about the content of usual care

(Table 2). Pharmacotherapy was the most frequently reported treatment method in usual care. See Table 2 for an overview of the percentage of patients receiving pharmacotherapy, appropriate pharmacotherapy, counselling, CBT and (specialised) mental health care as reported in the included studies.

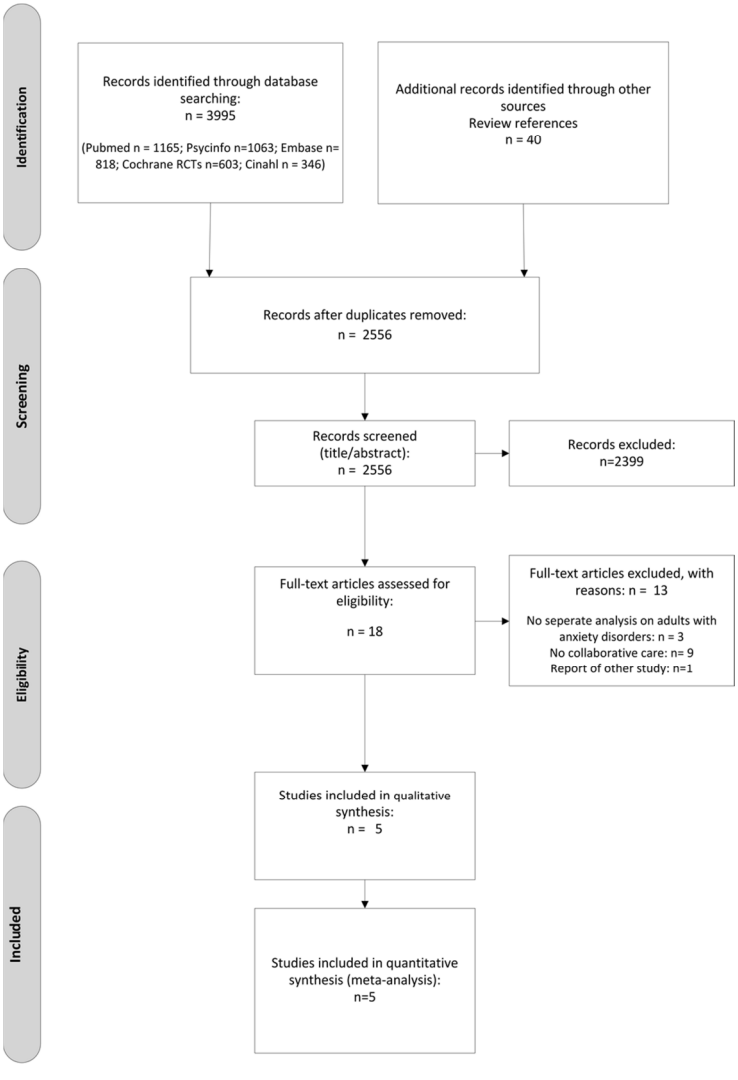

Figure 1. Prisma flowchart. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table 1. Characteristics of included studies

Study	Design	Recruit-ment	Diagn instr.	Int.	Setting	*N (ITT)*	Collaborative care intervention	Prof. involved	Outcomes FU	Outcome CC vs CAU	Outcome at 12 months [95% CI]
Roy-Byrne et al. 2001	RCT	Referral Screening (PHQ-2 PD)	PD CIDI	CC vs CAU	3 primary care clinics (US)	CC: 57 CAU: 58	Medication, educational video, 2 visits and 2 phone calls psychiatrist, 5 follow-up calls by psychiatrist	PCP, psychia–trist	ASI, PDSS 3,6,9,12 months	-Improved anxiety outcome at 3,6 and 12 months -Improved panic outcome at 6 months	-Anxiety/panic (ASI): $F_{1,82}$=4.60, p = 0.035 ES 0.40 [0.03-0.77] -Panic (PDSS): statistics continuous outcome not reported
Roy-Byrne et al. 2005	RCT	Referral Screening (PHQ-2 PD)	PD CIDI	CC vs CAU	University affiliated primary care clinics (US)	CC: 119 CAU: 113	CBT 6 sessions and 6 telephone follow-up contacts by CM, educati-onal video and workbook, medication, supervision of CM by psychiatrist	PCP, CM, psychia–trist	ASI 3,6,9,12 months	-Improved anxiety/panic outcome at all time points	-Anxiety/panic (ASI): Diff -6.64 [-10.73 to -2.48] p <0.001; ES 0.44 [0.18-0.70]
Rollman et al. 2005	RCT	Screening (PHQ)	PD/ GAD PRIME-MD	CC vs CAU	4 university affiliated primary care practices (US)	CC: 116 CAU: 75	Choice of self management with workbook and CM tel. contacts; medication; referral to ment. health spec. Tel. follow-up by CM, supervision of CM by psychiatrist	PCP, CM, psychia–trist/ Psycho-therapist	SIGH-A, PDSS 2,4,8,12 months	-Improved anxiety outcome at 12 months - Improved panic outcomes at 12 months -No sign. improvement in GAD outcomes	-Anxiety (SIGH-A): Diff -3.6 [-6.4 to -0.8] p = 0.01; ES 0.39 [0.09-0.68] -Panic (PDSS): Diff -3.3 [-5.5 to -1.1] p = 0.004; ES 0.57 [0.18-0.96] -GAD (SIGH-A): Diff -1.1 [-5.0 to 2.7] p = 0.57; ES 0.13 [-0.32 to 0.58]
Konig et al 2009	Cluster RCT	Screening (PHQ)	PD/ GAD/ any AD PHQ	CC vs CAU	46 primary care practices in Germany	CC: 201 CAU: 188	CBT by the PCP with the opportunity of in-practice psychiatric consultation	PCP, psychia–trist/ Psycho-therapist	BAI 6,9 months	- No difference in anxiety outcomes	-Anxiety (BAI): CC: M 18.18 SD 12.17 CAU: M 16.72 SD 10.34, p = 0.35; ES -0.13 [-0.36-0.99]

Study	Design	Recruit-ment	Diagn instr.	Int.	Setting	*N (ITT)*	Collaborative care intervention	Prof. involved	Outcomes FU	Outcome CC vs CAU	Outcome at 12 months [95% CI]
Roy-Byrne et al 2010 US	RCT	Referral	PD/ GAD/ SP/ PTSD MINI	CC vs CAU	17 primary care clinics (US)	CC: 503 CAU: 501	Choice of 6 sessions computerized CBT guided by the CM and/or medication, monitoring and monthly follow-up by the CM, supervision of CM by psychiatrist, IT support	PCP, CM, psychia–trist	ASI, PDSS, GADSS, SPIN, PCL-C 6,12,18 months	-Improved anxiety outcome at all time points -Improved panic outcome at 6 and 12 months -Improved GAD outcome at all time points -Improved SP outcome at 6 and 12 months -No sign. improvement in PTSD outcomes	-Anxiety (ASI): Diff -4.74 [-6.55 to -2.93] p <0.001; ES 0.32 [0.0.20-0.45] -Panic (PDSS): Diff −2.71 [−4.29 to −1.14] p= .003; ES 0.42 [0.17-0.66] -GAD (GADSS): Diff -2.34 [-3.22 to -1.45] p <0.001; ES 0.44 [0.27 to 0.61] -SP (SPIN): Diff -5.71 [-10.74 to -0.68] p = 0.08; ES 0.39 [0.04 to 0.74] -PTSD (PCL-C): Diff -7.7 [-17.55 to 2.15] p = 0.49; ES 0.39 [-0.12 to 0.90]

Abbreviations: AD: anxiety disorder; ASI: Anxiety Sensitivity Index; CAU: care as usual; CBT: cognitive behavioural therapy; CC: collaborative care; CI: confidence interval; CIDI: Composite International Diagnostic Interview; CM: care manager; ES: effect size; GAD: generalized anxiety disorder; GADSS: Generalised Anxiety Disorder Severity Scale; GER: Germany; ITT: intention to treat; MINI: Mini-International Neuropsychiatric Interview; PD: Panic disorder; PCL-C: PTSD Checklist–Civilian Version; PCP: primary care physician; PDSS: panic disorder severity scale; PHQ: Patient Health Questionnaire; PRIME-MD: Primary Care Evaluation of Mental Disorders; PTSD: post traumatic stress disorder; SIGH-A: Hamilton Anxiety Rating Scale; SP: social phobia; SPIN: Social Phobia Inventory; US: United States;

Table 2. Care received in the collaborative care and care as usual conditions

Content of care*	**Pharmaco-therapy (%)**		**Approriate pharmaco therapy (%)**		**Counselling (%)**		**CBT (%)**		**Referral to ment. health prof. (%)**	
Study	CC	CAU	CC	CAU	CC	CAU	CC	CAU	CC	CAU
Roy-Byrne et al. 2001	77%[a]	48%[a]	47%[b]	33%[b]	NA	NA	NA	NA	NA	25%
Roy-Byrne et al. 2005b	54%[c]	52%[c]	41%[b]	39%[b]	70%	34%	63%[d]	14%[d]	NA	NA
Rollman et al. 2005	77%[e]	66%[e]	NA	NA	79%[f]	NA	66%[g]	NA	18%	26%
König et al. 2009	NA	NA	NA	NA	NA	NA	NA	NA	33%	33%
Roy-Byrne et al. 2010	70%[h]	68%[h]	46%[i]	42%[i]	88%	51%	82%[j]	34%[j]	NA	NA

*Highest % of patients that have received a form of care at any follow-up measurement

[a] Appropriate type of medication

[b] Adequate type, dose and duration of medication

[c] Any antipanic pharmacotherapy

[d] 3 or more sessions counselling plus at least 4 of 7 CBT techniques

[e] SSRI/SNRI pharmacotherapy

[f] 3 or more telephone contacts with CM

[g] 3 or more telephone contacts with CM about CBT workbook

[h] Any psychotropic medication

[I] Appropriate type, dose and duration

[j] Counselling with at least 3 CBT elements

NA=Not Available

3.2.5 Outcome measures

All studies included a continuous outcome to measure general anxiety, although different scales were used. Three studies (Roy-Byrne *et al.* 2010; 2005b; 2001) used the Anxiety Sensitivity Index as an outcome measure (ASI (Reiss *et al.* 1986)), one study (Rollman *et al.* 2005) used a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A (Shear *et al.* 2001)), and one study (König *et al.* 2009) used the Beck Anxiety Inventory (BAI (Beck *et al.* 1988)). Besides a general anxiety measure, four studies reported separately about panic disorder outcomes (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; 2005b; 2001). Two of these studies reported panic outcomes on a panic disorder specific scale, the Panic Disorder Severity Scale (PDSS, (Shear *et al.* 1997), Rollman *et al.* 2005; Roy-Byrne *et al.* 2001). However, Roy-Byrne and colleagues (2001) did only report a non-significant outcome on the PDSS without data necessary to calculate the effect size. Roy-Byrne and colleagues (2010) reported PDSS outcomes for patients with panic disorder in a separate paper (Craske *et al.* 2011), where also disorder specific outcomes for social phobia, generalised anxiety disorder and posttraumatic stress disorder were reported. Rollman and colleagues (2005) reported separate outcomes for patients with generalised anxiety disorder. The length of follow-up varied from 9 months (König *et al.* 2009) to 18 months (Roy-Byrne *et al.* 2010). König and colleagues (2009) collected the outcome measures by mail (self-report), while in the other four studies a (blinded) research assistant administered the outcome measures by telephone.

3.3 Risk of bias

Table 3 shows that the risk of bias varied between studies. The most prevalent source of bias was the inability to blind patients and professionals for treatment allocation, as is common in psychotherapy research (Van der Feltz-Cornelis & Ader 2000). Furthermore, one trial (Roy-Byrne *et al.* 2001) did not provide the statistics of an insignificant result on the panic outcome. Of three studies, a published study protocol was retrieved: Roy-Byrne and colleagues (2005b) (Craske *et al.* 2002)), Rollman and colleagues (2005) (Rollman *et al.* 2003) and Roy-Byrne and colleagues (2010) (Sullivan *et al.* 2007).

Table 3. Risk of bias of included studies

	Roy-Byrne et al. 2001	Roy-Byrne et al. 2005b	Rollman et al. 2005	König et al. 2009	Roy-Byrne et al. 2010
Adequate sequence generation?	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Allocation concealed?	Unclear risk	Low risk	Low risk	Low risk	Low risk
Patients blinded?	Unclear risk	High risk	High risk	Low risk	Unclear risk
Professionals blinded?	Unclear risk	High risk	High risk	Low risk	Unclear risk
Outcome assessors blinded?	Low risk	Low risk	Low risk	Unclear risk	Low risk
Incomplete outcome data addressed?	Unclear risk	Low risk	Low risk	Low risk	Low risk
Free of selective reporting?	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Free of other bias	Unclear risk	Low risk	Low risk	Low risk	Low risk
Conclusion	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**	**Low risk**

3.4 Results of individual studies

The results of the individual studies at follow-up closest to 12 months are reported in Table 1. Four studies reported a larger effect of the collaborative care intervention compared to care as usual (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; 2005b; 2001). Conversely, König and colleagues (2009) could not demonstrate a higher effectiveness of the intervention compared to care as usual. The effect sizes varied from -0.13 (König *et al.* 2009) to 0.44 (Roy-Byrne *et al.* 2005b). The effects of collaborative care compared to care as usual for patients with an anxiety disorder were statistically summarised using meta-analysis (Figure 2). The pooled effect size of all five studies

was 0.27 (95% CI 0.07 to 0.48, p=0.009). This means that, combining the existing studies about collaborative care for anxiety disorders compared to care as usual, collaborative care leads to a significantly larger reduction in anxiety symptoms, with a small clinical relevance after 12 months. The *Q*-value was 15.08 (df=4, p=0.005) indicating significant dispersion across studies. The I^2 was 73.5%, which indicates that a high proportion of the total variation may be attributed to true heterogeneity between studies. Retrospective exploration of the heterogeneity revealed that the study of König and colleagues (2009) differed markedly from the other four studies in design, setting, intervention and outcome. When we excluded this study from the meta-analysis the combined effect of the four studies was 0.35 (95% CI 0.30 to 0.47), with a *Q*-value of 0.72 (df=3, p=0.87) and a I^2 of 0%. This means that in this analysis, excluding the study of König and colleagues (2009), the effect size was moderate and heterogeneity between studies was low.

Study	Std diff in means	Std error	Lower limit	Upper limit	Z	p
Roy-Byrne et al. 2001	0.398	0.188	0.029	0.767	2.113	0.035
Roy-Byrne et al. 2005	0.438	0.133	0.177	0.698	3.294	0.001
Rollman et al. 2005	0.386	0.149	0.093	0.679	2.579	0.010
König et al. 2009	-0.129	0.117	-0.358	0.099	-1.108	0.268
Roy-Byrne et al. 2010	0.324	0.064	0.199	0.449	5.100	0.000
Total	**0.272**	**0.105**	**0.067**	**0.478**	**2.596**	**0.009**

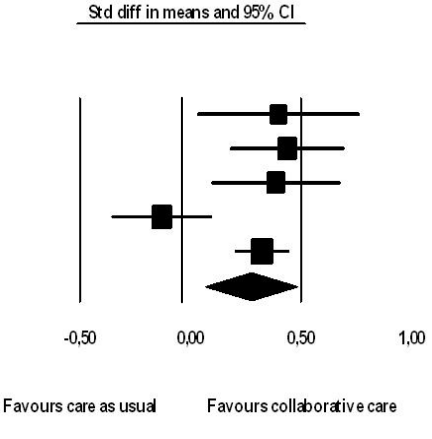

Figure 2. Meta-analysis for the effect of collaborative care versus care as usual for patients with an anxiety disorder at 12 months follow-up

3.5 Additional analysis: disorder specific impact of collaborative care

A pre-envisioned subgroup analysis was performed for patients with panic disorder. Outcomes on the Panic Disorder Severity Scale (PDSS) were used when reported. For the study that did not report the PDSS (Roy-Byrne *et al.* 2005b), the ASI was used as

outcome measure in the meta-analysis. Because Roy-Byrne and colleagues (2001) did only report that they found an insignificant result on the PDSS, but did not report the statistics necessary for calculating the effect size, we used the ASI score as well. However, this may lead to an overestimation of the effect, because the ASI did show significant results, while the PDSS did not. Figure 3 shows that the combined effect size of the four studies comparing collaborative care to care as usual in patients with panic disorder was 0.44 (95% CI 0.30 to 0.59, p<0.001), which may be interpreted as a moderate effect size.

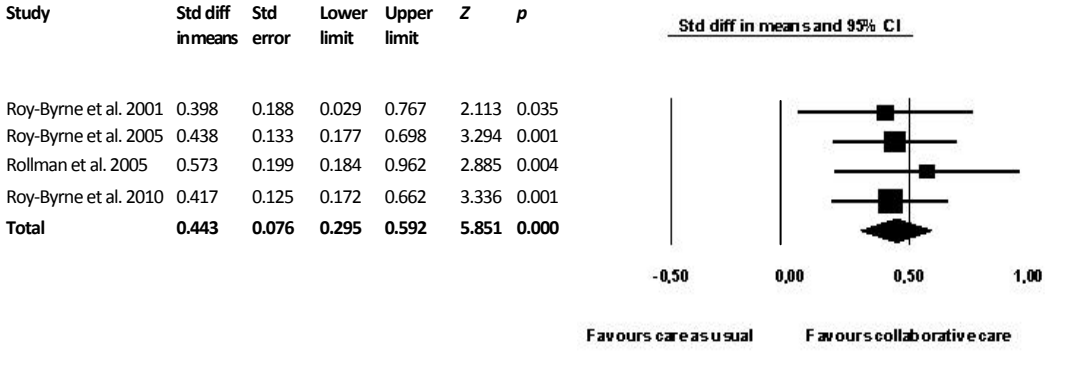

Figure 3. Subgroup-analysis of the effect of collaborative care versus care as usual for patients with panic disorder at 12 months follow-up

A meta-analysis on the effects of collaborative care for anxiety disorders other than panic disorder was not performed, because only two studies reported separate outcomes for anxiety disorders other than panic disorder (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010). In the study of Rollman and colleagues (2005) no significant effect was found for patients with generalised anxiety disorder only. Roy-Byrne and colleagues (2010) did report the outcomes of patients with panic disorder, generalised anxiety disorder, social phobia and posttraumatic stress disorder (PTSD). The authors reported significant effects on the ASI at 12 months for all anxiety disorders except for PTSD. In a subsequent report (Craske *et al.* 2011), disorder specific data on specific scales were reported, with similar results. See Table 1 for a summary of the data.

3.6 Additional analysis: impact of the inclusion of a care manager

A meta-regression (Figure 4) was performed to assess the impact of the inclusion of a care manager in the collaborative care model on the effect size. Two studies (Roy-Byrne *et al.* 2001; König *et al.* 2009) did only include a psychiatrist and a primary care physician and three studies did include a care manager, psychiatrist and a primary care physician (Roy-Byrne *et al.* 2010; 2005b; Rollman *et al.* 2005). This explorative analysis revealed a significant positive effect of the inclusion of a care manager on effect size (b=0.33, 95% CI 0.11-0.55). However, because of the low number of studies and the variation in effect size between the two studies without a care manager, this explorative analysis should be interpreted with caution.

3.7 Publication bias

Using Duval and Tweedie's trim and fill method (Duval & Tweedie 2000) we examined the possibility of publication bias and the estimated effect of publication bias on the effect size. The funnel plot (Figure 5) shows that there was an indication of publication bias for studies considering all anxiety disorders, in which case the effect size would be adjusted from 0.27 to 0.25 (95% CI 0.054 to 0.42) for the main analysis. This may indicate that there is some evidence that the effect of collaborative care for anxiety disorders is slightly overestimated due to publication bias. However, the adjustment for this possible bias is minimal and after adjustment there is still a significant positive effect. Furthermore, the asymmetry may be caused as well by true heterogeneity between studies (Sterne *et al.* 2011) mainly attributable to the negative result of one study (König *et al.* 2009). For the sub-group analysis on panic disorder, there were no indications for publication bias (Figure 6) and the effect size was not adjusted according to the trim and fill method.

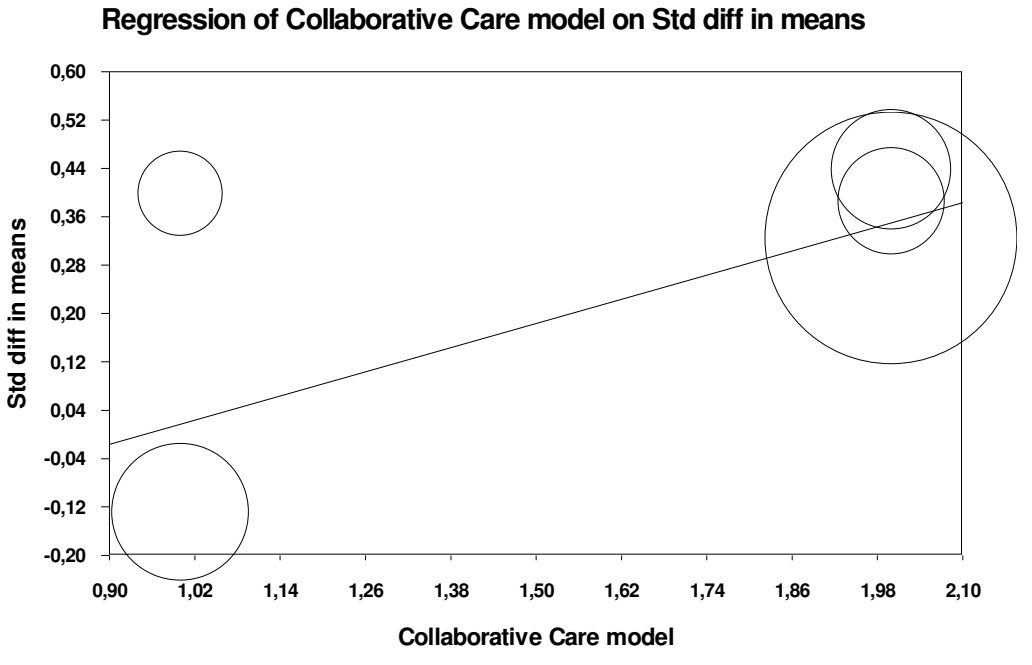

Figure 4. Meta-regression analysis of the impact of the inclusion of a care manager in the collaborative care model (without care manager (1) vs. with care manager (2)) on the effect size of studies.

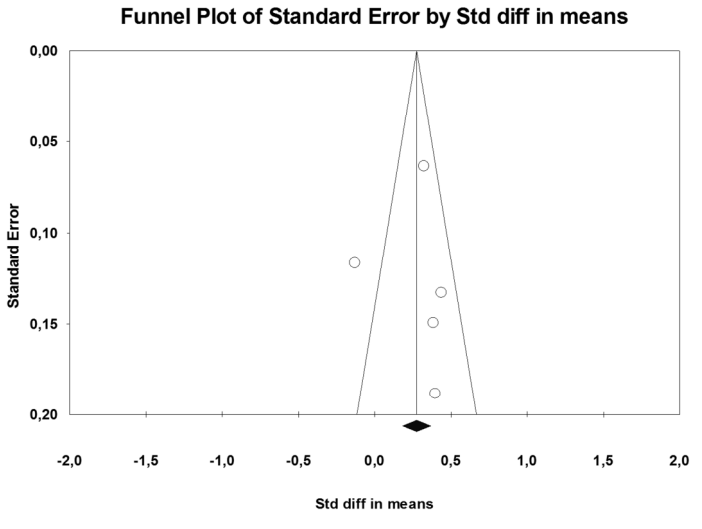

Figure 5. Funnel plot for studies reporting on anxiety disorders

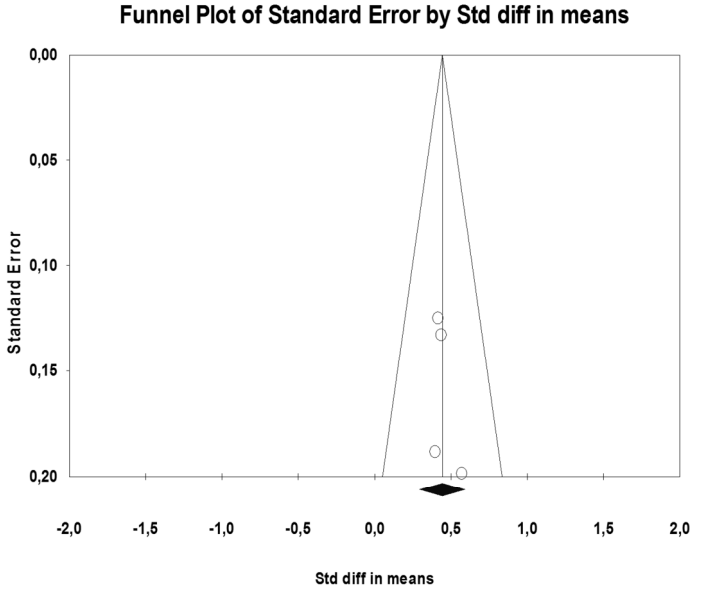

Figure 6. Funnel plot for studies reporting on panic disorders

4 Discussion

4.1 Summary of evidence

The results of this systematic review and meta-analysis indicate that collaborative care is more effective than usual primary care for patients with anxiety disorders at twelve months follow-up, particularly for patients with panic disorder. The number of studies identified was small, studies were almost exclusively conducted in the United States and panic disorder was the only anxiety disorder that could be evaluated separately. The risk of bias of included studies varied. Models including a care manager might be more effective.

4.2 Strengths and limitations

A strength of this study is that, to our knowledge, this is the first meta-analysis on collaborative care for anxiety disorders. We conducted the review using PRISMA criteria (Liberati *et al.* 2009). Furthermore, we were able to examine the long-term effects of collaborative care, which is a strength because long-term results are often lacking in effectiveness studies on anxiety disorders in primary care (Seekles *et al.* 2012). Because all studies used an anxiety scale as outcome measure, we were able to accurately combine results. However, there are several limitations in this systematic review and meta-analysis that need consideration.

We identified only five studies that met our inclusion criteria. As our search was limited to published articles we may have missed RCTs that were unpublished, which may have resulted in an overestimation of the effect of collaborative care interventions (Hopewell *et al.* 2009). Furthermore, because one study (Roy-Byrne *et al.* 2001) did not report the statistics for the insignificant effect on the panic specific measure, the effect in the sub-group analysis on panic disorder may have been slightly overestimated.

Caution is warranted for any conclusions about the effectiveness of collaborative care for anxiety disorders other than panic disorder because only two studies reported separate outcomes for other anxiety disorders than panic disorder and the results of these studies were inconsistent (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010).

The results of this systematic review and meta-analysis are limited to results found after twelve months. Effects may either be larger (Roy-Byrne *et al.* 2001) or smaller before 12 months (Rollman *et al.* 2005). Roy-Byrne and colleagues (2010) reported a smaller (but significant) effect size after 18 compared to 12 months.
The concentration of studies in primary care settings in the United States may limit the external validity of the results. In depression research however, no evidence was found for a different effect of collaborative care across settings or countries (Thota *et al.* 2012).

4.3 Comparison with the literature

The small number of studies identified is in sharp contrast with the bulk of studies conducted in the field of depression research. Nevertheless, the combined effect size of 0.27 found in this first meta-analysis of the effects of collaborative care for anxiety disorders is similar to the effect size of 0.25 (Gilbody *et al.* 2006) for depressive disorders. Our meta-analysis is a first indication that collaborative care for anxiety disorders may be as effective as collaborative care for depressive disorders.
A meta-regression in the study of Gilbody and colleagues (2006) suggested that collaboration between a care manager and primary care physician with access to specialist input led to a higher effectiveness than care management alone, although the effect was not significant. We compared care management with access to specialist input with specialist input alone (collaboration with a psychiatrist) and found a significantly better effect for studies using care management with specialist input. However, the number of studies in our review was too small to adequately interpret this finding. The study of König and colleagues (2009) was the only study that did not report a significant effect of the intervention, probably due to a suboptimal implementation of the intervention. König and colleagues (2009) suggest that adding patient education and a basic package of specialised mental health care may improve outcomes, which may be seen as a more elaborate form of collaborative care.
The adequacy of pharmacotherapy in the usual care conditions in the included studies from the United States seems to be higher than what has been reported in the literature (Young *et al.* 2001; Wang *et al.* 2005; Stein *et al.* 2011). This may indicate that the physicians participating in these trials were not representative of all physicians in

the United States, or that a contamination of the effect has occurred (Richards *et al.* 2008). The relatively high quality of pharmacotherapy in the usual care conditions in the American studies may have resulted in conservative estimates of the effectiveness of collaborate care.

4.4 Implications for practice

The first trials on collaborative care for anxiety disorders indicate that collaborative care may significantly improve patient outcomes in primary care, at least in settings in the United States. Although the effectiveness of collaborative care is unclear for other settings, it is promising that the trials considering anxiety disorders show similar results as the trials considering depressive disorders which have also been conducted outside the United States (Gilbody *et al.* 2006; Thota *et al.* 2012). However, to achieve successful implementation in daily practice, efforts are needed to train, reimburse and guide care managers, primary care physicians and supervising psychiatrists to implement collaborative care (Lauren Crain *et al.* 2012).

4.5 Implications for research

Most importantly, more research is needed on collaborative care for anxiety disorders in primary care. Randomised controlled trials are warranted in settings outside the United States and that focus on anxiety disorders other than panic disorder. Information about the (very) long-term effects and the cost-effectiveness of collaborative care for anxiety disorders is also needed. Furthermore, it would be useful for decision making if collaborative care and care as usual conditions were described in a standardised manner in randomised controlled trials (Boutron *et al.* 2008) to facilitate interpretation of the findings and comparison across studies.

4.6 Conclusion

This systematic review and meta-analysis evaluated the existing literature and found that collaborative care in primary care is effective for adult patients with panic disorder and may be effective for patients with other anxiety disorders compared to care as usual. More research is needed to evaluate the effectiveness of collaborative care in different settings and different anxiety disorders.

REFERENCES

Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* **56 (6)**, 893-897.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & M.Rothstein HR (2009). *Introduction to Meta-Analysis (Statistics in Practice)*. Wiley & Sons:

Borenstein, M., Hedges, L. V., Higgins, J. P. T. & Rothstein, H. R. (2005). Comprehensive Meta-Analysis, Version 2. *Biostat* **Englewood NJ, USA**.

Boutron, I., Moher, D., Altman, D. G., Schulz, K. F. & Ravaud, P. (2008). Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* **148**, 295-309.

Bower, P., Gilbody, S., Richards, D., Fletcher, J. & Sutton, A. (2006). Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. *British Journal of Psychiatry* **189**, 484-493.

Cape, J., Whittington, C., Buszewicz, M., Wallace, P. & Underwood, L. (2010). Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. *BMC Med* **8**, 38.

Cohen, J. (1988). *Statistical power analysis for the behavioral science. Second Edition.* Lawrence Erlbaum Associates,Inc.: Hillsdale.

Craske, M. G., Roy-Byrne, P., Stein, M. B., Donald-Sherbourne, C., Bystritsky, A., Katon, W. & Sullivan, G. (2002). Treating panic disorder in primary care: a collaborative care intervention. *General Hospital Psychiatry* **24 (4)**, 148-155.

Craske, M. G., Stein, M. B., Sullivan, G., Sherbourne, C., Bystritsky, A., Rose, R. D., Lang, A. J., Welch, S., Campbell-Sills, L., Golinelli, D. & Roy-Byrne, P. (2011). Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. *Arch Gen Psychiatry* **68**, 378-388.

Duval, S. & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455-463.

Fernandez, A., Haro, J. M., Martinez-Alonso, M., Demyttenaere, K., Brugha, T. S., Autonell, J., De Girolamo, G., Bernert, S., Lepine, J. P. & Alonso, J. (2007). Treatment adequacy for anxiety and depressive disorders in six European countries. *Br J Psychiatry* **190**, 172-173.

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch.Intern.Med.* **166**, 2314-2321.

Gilbody, S., Whitty, P., Grimshaw, J. & Thomas, R. (2003). Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *Jama* **289**, 3145-3151.

Grembowski, D. E., Martin, D., Patrick, D. L., Diehr, P., Katon, W., Williams, B., Engelberg, R., Novak, L., Dickstein, D., Deyo, R. & Goldberg, H. I. (2002). Managed care, access to mental health specialists, and outcomes among primary care patients with depressive symptoms. *J Gen Intern Med* **17**, 258-269.

Heideman, J., van, R. E., van, L. N., de, L. S., Laurant, M., Wensing, M., van de Lisdonk, E. & Grol, R. (2005). Interventions to improve management of anxiety disorders in general practice: a systematic review. *Br J Gen Pract* **55**, 867-874.

Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj* **327**, 557-560.

Higgins, J. P. T., Altman, G., & Sterne, A. C. (2011). Assessing risk of bias in included studies. In *Cochrane handbook of systematic reviews of interventions. Version 5.1.0.* (eds. J. P. T. Higgins and S. Green). The Cochrane Collaboration.

Higgins, J. P. T. & Deeks, J. J. (2011). Selecting studies and collecting data. In *Cochrane handbook for systematic reviews of interventions. Version 5.1.0.* (eds. J. P. T. Higgings and S. Green). The Cochrane Collaboration.

Hopewell, S., Loudon, K., Clarke, M. J., Oxman, A. D. & Dickersin, K. (2009). Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane database of systematic reviews (Online)*.

Katon, W., Von, K. M., Lin, E. & Simon, G. (2001). Rethinking practitioner roles in chronic illness: the specialist, primary care physician, and the practice nurse. *Gen.Hosp.Psychiatry* **23**, 138-144.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R. & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 617-627.

Kessler, R. C., Ruscio, A. M., Shear, K. & Wittchen, H. U. (2010). Epidemiology of anxiety disorders. *Curr Top Behav Neurosci* **2**, 21-35.

König, H. H., Born, A., Heider, D., Matschinger, H., Heinrich, S., Riedel-Heller, S. G., Surall, D., Angermeyer, M. C. & Roick, C. (2009). Cost-effectiveness of a primary care model for anxiety disorders. *Br J Psychiatry* **195**, 308-317.*

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O. & Lowe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann.Intern.Med* **146**, 317-325.

Lauren Crain, A., Solberg, L. I., Unutzer, J., Ohnsorg, K. A., Maciosek, M. V., Whitebird, R. R., Beck, A. & Molitor, B. A. (2012). Designing and Implementing Research on a Statewide Quality Improvement Initiative: The DIAMOND Study and Initiative. *Med Care*.

Lepine, J. P. (2002). The epidemiology of anxiety disorders: prevalence and societal costs. *J Clin Psychiatry* **63 Suppl 14**, 4-8.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J. & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Plos Medicine, 2009 Jul 21; Vol.6 (7)*.

Nutting, P. A., Rost, K., Dickinson, M., Werner, J. J., Dickinson, P., Smith, J. L. & Gallovic, B. (2002). Barriers to initiating depression treatment in primary care practice. *J Gen Intern Med* **17**, 103-111.

Prins, M. A., Verhaak, P. F., Bensing, J. M. & van der, M. K. (2008). Health beliefs and perceived need for mental health care of anxiety and depression--the patients' perspective explored. *Clin Psychol Rev* **28**, 1038-1058.

Reiss, S., Peterson, R. A., Gursky, D. M. & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther* **24**, 1-8.

Rhebergen, D., Batelaan, N. M., de Graaf, R., Nolen, W. A., Spijker, J., Beekman, A. T. F. & Penninx, B. W. J. H. (2011). The 7-year course of depression and anxiety in the general population. *Acta Psychiatr Scand* **123**, 297-306.

Richards, D. A. (2012). Stepped care: a method to deliver increased access to psychological therapies. *Can J Psychiatry* **57**, 210-215.

Richards, D. A., Lovell, K., Gilbody, S., Gask, L., Torgerson, D., Barkham, M., Bland, M., Bower, P., Lankshear, A. J., Simpson, A., Fletcher, J., Escott, D., Hennessy, S. & Richardson, R. (2008). Collaborative care for depression in UK primary care: a randomized controlled trial. *Psychological Medicine* **38**, 279-287.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.*

Rollman, B. L., Herbeck, B. B., Reynolds, C. F., Schulberg, H. C. & Shear, M. K. (2003). A contemporary protocol to assist primary care physicians in the treatment of panic and generalized anxiety disorders. *Gen Hosp.Psychiatry* **25**, 74-82.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.*

Roy-Byrne, P. P., Wagner, A. W. & Schraufnagel, T. J. (2005a). Understanding and treating panic disorder in the primary care setting. *Journal of Clinical Psychiatry* **66 Suppl 4**, 16-22.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005b). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.*

Roy-Byrne, P. P., Katon, W., Cowley, D. S. & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* **58**, 869-876.*

Seekles, W., Cuijpers, P., Kok, R., Beekman, A., van, M. H. & van, S. A. (2012). Psychological treatment of anxiety in primary care: a meta-analysis. *Psychol Med*, 1-11.

Shear, M. K., Brown, T. A., Barlow, D. H., Money, R., Sholomskas, D. E., Woods, S. W., Gorman, J. M. & Papp, L. A. (1997). Multicenter collaborative panic disorder severity scale. *Am J Psychiatry* **154**, 1571-1575.

Shear, M. K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W., Pollack, M. H., Chandler, L., Williams, J., Ali, A. & Frank, D. M. (2001). Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety* **13**, 166-178.

Smolders, M., Laurant, M., Roberge, P., Van Balkom, A., Van Rijswijk, E., Bower, P. & Grol, R. (2008). Knowledge transfer and improvement of primary and ambulatory care for patients with anxiety. *Can J Psychiatry* **53**, 277-293.

Smolders, M., Laurant, M., Verhaak, P., Prins, M., van Marwijk, H., Penninx, B., Wensing, M. & Grol, R. (2010). Which physician and practice characteristics are associated with adherence to evidence-based guidelines for depressive and anxiety disorders? *Med Care* **48**, 240-248.

Stein, M. B., Roy-Byrne, P. P., Craske, M. G., Campbell-Sills, L., Lang, A. J., Golinelli, D., Rose, R. D., Bystritsky, A., Sullivan, G. & Sherbourne, C. D. (2011). Quality of and patient satisfaction with primary health care for anxiety disorders. *J Clin Psychiatry* **72**, 970-976.

Sterne, J. A. C., Egger, M., & Moher, B. (2011). Addressing reporting bias. In *Cochrane handbook for systematic reviews of interventions. Version 5.1.0.* (eds. J. P. T. Higgins and S. Green). The Cochrane Collaboration.

Sullivan, G., Craske, M. G., Sherbourne, C., Edlund, M. J., Rose, R. D., Golinelli, D., Chavira, D. A., Bystritsky, A., Stein, M. B. & Roy-Byrne, P. P. (2007). Design of the Coordinated Anxiety Learning and Management (CALM) study: innovations in collaborative care for anxiety disorders. *General Hospital Psychiatry, 2007 Sep-Oct; Vol.29 (5), pp.379-87.*

Taylor, S., Abramowitz, J. & Mckay, D. (2012). Non-adherence and non-response in the treatment of anxiety disorders. *J Anxiety Disord.*

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease, D. E., Jr. & Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med* **42**, 525-538.

van Beljouw, I., Verhaak, P., Prins, M., Cuijpers, P., Penninx, B. & Bensing, J. (2010). Reasons and determinants for not receiving treatment for common mental disorders. *Psychiatr Serv* **61**, 250-257.

Van der Feltz-Cornelis, C. M. & Ader, H. J. (2000). Randomization in psychiatric intervention research in the general practice setting. *International Journal of Methods in Psychiatric Research* **9**, 134-142.

van Geffen, E. C. G., Gardarsdottir, H., van Hulten, R., van Dijk, L., Egberts, A. C. G. & Heerdink, E. R. (2009). Initiation of antidepressant therapy: do patients follow the GP's prescription? *Br J Gen Pract* **59**, 81-87.

van Marwijk, H. (2004). How to improve mental health competency in general practice training?--a SWOT analysis. *Eur J Gen Pract* **10**, 61-65.

van Steenbergen-Weijenburg, K. M., van der Feltz-Cornelis CM, Horn, E. K., van Marwijk, H. W., Beekman, A. T., Rutten, F. F. & Hakkaart-van, R. L. (2010). Cost-effectiveness of collaborative care for the treatment of major depressive disorder in primary care. A systematic review. *BMC Health Services Research, 2010; Vol.10, pp.19.*

Von Korff, M., Gruman, J., Schaefer, J., Curry, S. J. & Wagner, E. H. (1997). Collaborative management of chronic illness. *Ann Intern.Med* **127**, 1097-1102.

Wagner, E. H., Austin, B. T., Davis, C., Hindmarsh, M., Schaefer, J. & Bonomi, A. (2001). Improving chronic illness care: translating evidence into action. *Health Aff.(Millwood.)* **20**, 64-78.

Wampold, B. E., Budge, S. L., Laska, K. M., Del Re, A. C., Baardseth, T. P., Fluckiger, C., Minami, T., Kivlighan, D. M. & Gunn, W. (2011). Evidence-based treatments for depression and anxiety versus treatment-as-usual: A meta-analysis of direct comparisons. *Clin Psychol Rev* **31**, 1304-1312.

Wang, P. S., Lane, M., Olfson, M., Pincus, H. A., Wells, K. B. & Kessler, R. C. (2005). Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**, 629-640.

Young, A. S., Klap, R., Sherbourne, C. D. & Wells, K. B. (2001). The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry* **58**, 55-61.

* Studies included in review

Chapter 3

Study a

Collaborative stepped care for anxiety disorders in primary care: aims and design of a randomised controlled trial

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Abstract

Background: Panic disorder (PD) and generalised anxiety disorder (GAD) are two of the most disabling and costly anxiety disorders seen in primary care. However, treatment quality of these disorders in primary care generally falls beneath the standard of international guidelines. Collaborative stepped care is recommended for improving treatment of anxiety disorders, but cost-effectiveness of such an intervention has not yet been assessed in primary care. This article describes the aims and design of a study that is currently underway. The aim of this study is to evaluate effects and costs of a collaborative stepped care approach in the primary care setting for patients with PD and GAD compared with care as usual.

Methods/design: The study is a two armed, cluster randomised controlled trial. Care managers and their primary care practices will be randomised to deliver either collaborative stepped care (CSC) or care as usual (CAU). In the CSC group a general practitioner, care manager and psychiatrist work together in a collaborative care framework. Stepped care is provided in three steps: 1) guided self-help, 2) cognitive behavioural therapy and 3) antidepressant medication. Primary care patients with a DSM-IV diagnosis of PD and/or GAD will be included. 134 completers are needed to attain sufficient power to show a clinically significant effect of ½ SD on the primary outcome measure, the Beck Anxiety Inventory (BAI). Data on anxiety symptoms, mental and physical health, quality of life, health resource use and productivity will be collected at baseline and after three, six, nine and twelve months.

Discussion: It is hypothesised that the collaborative stepped care intervention will be more cost-effective than care as usual. The pragmatic design of this study will enable the researchers to evaluate what is possible in real clinical practice, rather than under ideal circumstances. Many requirements for a high quality trial are being met. Results of this study will contribute to treatment options for GAD and PD in the primary care setting. Results will become available in 2011.

Trial registration: NTR1071

Background

Anxiety disorders are a great burden for patients, the general health system and society as a whole. Patients having an anxiety disorder suffer from considerable disability and reduced quality of life (Buist-Bouwman *et al.* 2006). In addition, anxiety disorders are associated with significant costs due to the use of health services and reduced productivity (Kessler *et al.* 2001).

Of the anxiety disorders, panic disorder (PD) and generalised anxiety disorder (GAD) are the most disabling (Cramer *et al.* 2005) and costly (Young *et al.* 2001; Wittchen *et al.* 2002; Andlin-Sobocki & Wittchen 2005) anxiety disorders that are frequently seen in primary care. Research has indicated that four to seven percent of primary care attendees suffer from one or both of these anxiety disorders (Roy-Byrne & Wagner 2004; Lieb *et al.* 2005; Roy-Byrne *et al.* 2005a; Kroenke *et al.* 2007).

As the majority of these patients is only seen in primary care (Young *et al.* 2001; Prins *et al.* 2008), this may be a convenient setting to treat these disorders. Treatment for PD and GAD can be highly effective (Gorman 2003; Otto & Deveney 2005). In recent decades the evidence for the effectiveness of treatments for anxiety disorders has been reviewed and described in clinical guidelines for treatment, where cognitive behavioural therapy as well as prescription of antidepressants are considered as the first choice of treatment for PD and GAD (Andrews *et al.* 2003; NHG 2004; The National Institute for Health and Clinical Excellence (NICE) 2007). However, these guidelines are rarely adhered to in primary care. About one third of patients with an anxiety disorder treated in primary care receive appropriate treatment as defined by a minimal accordance with existing guidelines (Young *et al.* 2001; Stein *et al.* 2004; Fernandez *et al.* 2007).

One of the reasons for the low quality of treatment is poor recognition of anxiety disorders. Even when compared to depression, the recognition rate of anxiety disorders is low, with about one third of anxiety disorder patients labelled as such by their general practitioner (GP) (Weiller *et al.* 1998; Wittchen & Hoyer 2001; Jackson *et al.* 2007). Several factors are involved in this low recognition rate, such as patients unwillingness or inability to discuss their anxiety problems with their GP (Mechanic 2007; Alonso *et al.* 2008; Prins *et al.* 2008) and limited knowledge of GPs about

psychiatric disorders. Moreover, GPs frequently work under time pressure and perceive they have not enough time to enquire about emotional problems. In conclusion, competing demands of the patient, the GP and the primary care structure of acute episodic care make diagnosing mental health problems difficult (Nutting *et al.* 2000).

Although ameliorating recognition of anxiety disorders is necessary (Ormel *et al.* 1991), it is not sufficient for improving primary health care for these patients (Mathias *et al.* 1994; Schulberg *et al.* 1997; Rollman *et al.* 2002). GPs often feel they do not have the necessary capabilities to treat these problems (van Boeijen *et al.* 2005b; Mechanic 2007). Moreover, the primary care system does not seem to be well organised for care for anxiety disorders (Ormel *et al.* 1991). As anxiety disorders often have a chronic nature (Yonkers *et al.* 2003), they make a poor fit with the acute disease model of primary care (Roy-Byrne *et al.* 2005a). Therefore, several researchers have proposed to use a chronic care model to implement evidence based care into practice. The most promising of these strategies are based on Wagner's model of care for chronic diseases (Wagner *et al.* 1996). This model was originally developed to improve treatment for chronic diseases like diabetes. The strategies following Wagner's model involve collaborative disease management with a pivotal role for a "care manager", who coordinates care, works according to an evidence-based treatment protocol, monitors treatment response and actively follows the patient. This care manager usually is a non-physician professional, who works in close collaboration with the GP. Care manager and GP are further assisted by a specialist from secondary care. This model was adopted for use with mental disorders, with a nurse practitioner or a psychologist as care manager and a psychiatrist functioning as consultant specialist (Katon *et al.* 1997; Katon *et al.* 2001).

This collaborative care model has been tested extensively in the treatment of depression, showing robust positive results (Gilbody *et al.* 2006; Bower *et al.* 2006). A few studies in the United States have investigated the effectiveness of collaborative care for anxiety disorders, especially PD (Roy-Byrne *et al.* 2001; Rollman *et al.* 2005; Roy-Byrne *et al.* 2005b) and GAD (Rollman *et al.* 2005). When compared to other strategies for improving care for anxiety disorders in ambulatory care, collaborative care seems to be the most effective (Smolders *et al.* 2008). In two of the studies

described above a cost-effectiveness analysis was performed. In both studies, collaborative care was more effective than care as usual. Results regarding cost-effectiveness were inconclusive, with collaborative care being either more or less costly than care as usual (Katon *et al.* 2002; Katon *et al.* 2006). Researchers of these collaborative care trials (Roy-Byrne *et al.* 2001) and international guidelines (The National Institute for Health and Clinical Excellence (NICE) 2007) recommend a stepped care approach for mental health care in primary care, with least invasive and costly interventions preceding more invasive and expensive forms of care. Such an approach may make collaborative care interventions more cost-effective.

This article describes the aims and methods of a randomised controlled trial to test the effectiveness of a collaborative stepped care intervention for PD and GAD in primary care in the Netherlands. Such a study is warranted for two reasons. First, there has been no study on the cost-effectiveness of a collaborative care intervention for anxiety disorders that includes a stepped care approach. Second, published studies about collaborative care for anxiety disorders all stem from the United States (US), where the collaborative care model was originally developed. As there are significant differences across health care systems in the US and in European countries (de Jong *et al.* 2009), the results of the collaborative care studies might not be generalised to other countries without consideration. To fill this gap in research, we designed a collaborative stepped care intervention for GAD and PD in the primary care setting. The treatment algorithm is built up from three interventions that have separately been proven effective and feasible in the primary care setting (van Boeijen *et al.* 2005b) (Van der Feltz-Cornelis *et al.* 2006). The interventions consist of guided self-help, cognitive behavioural therapy, and antidepressant medication (Van der Feltz-Cornelis *et al.* 2006). Other elements of collaborative care include a trained care manager (a mental health practice nurse or psychologist) who coordinates care and provides psychological treatment, the availability of a consultant psychiatrist for advising GP and care manager, telephone follow-up by the care manager and monitoring of anxiety symptoms to evaluate treatment progress and outcome. Effects and costs of the interventions will be assessed and an economic evaluation will be performed to estimate cost-effectiveness and cost-utility of the intervention. All relevant costs to

society associated with the burden of anxiety disorders will be taken into account. In accordance with the outcomes of similar previous studies, it is hypothesised that the collaborative stepped care intervention will be at least more effective and possibly less expensive than care as usual.

Methods/Design

Objectives

The primary aim of this randomised controlled trial (RCT) is to evaluate the effectiveness of collaborative stepped care (CSC) versus care as usual (CAU) in the treatment of panic disorder (PD) and generalised anxiety disorder (GAD) in primary care, with severity of anxiety symptoms as primary outcome measure. The secondary aim is to evaluate cost-effectiveness (costs of the intervention weighed against a reduction in anxiety symptoms) and to estimate cost-utility (costs of the intervention weighed against gained Quality Adjusted Life Years (QALY's)).

Study design

The study design is a two-armed, cluster randomised, controlled trial.

Time frame

This study was initiated in 2008 and will take three years. Results are expected in 2011.

Recruitment of GPs, care managers and psychiatrists

The study is designed in cooperation with the Netherlands Institute of Mental Health and Addiction (Trimbos Institute), the Department of General Practice and Psychiatry of the VU University Medical Centre in Amsterdam and the Department of Public Health and Primary Care of the Leiden University Medical Centre. GPs in the Leiden region that are located in the region of a large mental health centre (*Rivierduinen*) will receive an invitation to participate in the study, after which a researcher (AM) will contact all practices by phone to recommend participation. Participating practices will be able to decide which professional (e.g. a psychologist, a mental health practice nurse or a social worker) will fulfill the role of care manager. If the practice does not

have such a professional available, a mental health practice nurse working at the regional mental health centre will be available to work in the practice. Experienced psychiatrists working at the regional mental health centre will perform as consultant psychiatrists for the intervention practices.

Randomisation

Cluster randomisation will be applied at the level of the care manager to minimise contamination of the effect (Van der Feltz-Cornelis & Ader 2000). Randomisation will be performed using sequences obtained with an automated random sequence generation algorithm following a blocking scheme of variable length with allowance for restricted unbalance of at most three. Stratification will be on region, with six regions in total, which are based on working units of the regional mental health centre. The allocation sequences will be generated by an independent statistician (HA) in the manner described above. The care managers will be randomised and allocated to the intervention (CSC) or the control group (CAU). PCPs and GPs will be allocated to either CSC or CAU in accordance with the randomisation status of their care manager. After randomisation, neither care managers nor GPs will be blinded to group assignment. Figure 1 presents a flowchart of the recruitment and randomisation procedure.

Patient inclusion and exclusion criteria

Patients with a primary diagnosis of PD with or without agoraphobia and/or a primary diagnosis of GAD according to the criteria of the DSM IV (2001) will be included in the study. Patients who are suicidal, suffer from dementia or other severe cognitive disorders, psychotic disorder, bipolar disorder, dependence on drugs or alcohol, or with an unstable severe medical condition as diagnosed by their GP or as assessed in a diagnostic interview will be excluded. Patients with insufficient knowledge of the Dutch language to fill out the questionnaires, patients who are already receiving intensive psychological treatment (>2 contacts per month with a psychologist or psychiatrist) and patients who are under 18 years of age will also be excluded from the study. For reasons of generalisation, no other exclusion criteria are used. Having received treatment for anxiety problems in the past, using medication

(e.g. antidepressants or benzodiazepines) or a diagnosis of co-morbid psychiatric and medical conditions (except for those described above) will not be reasons for exclusion.

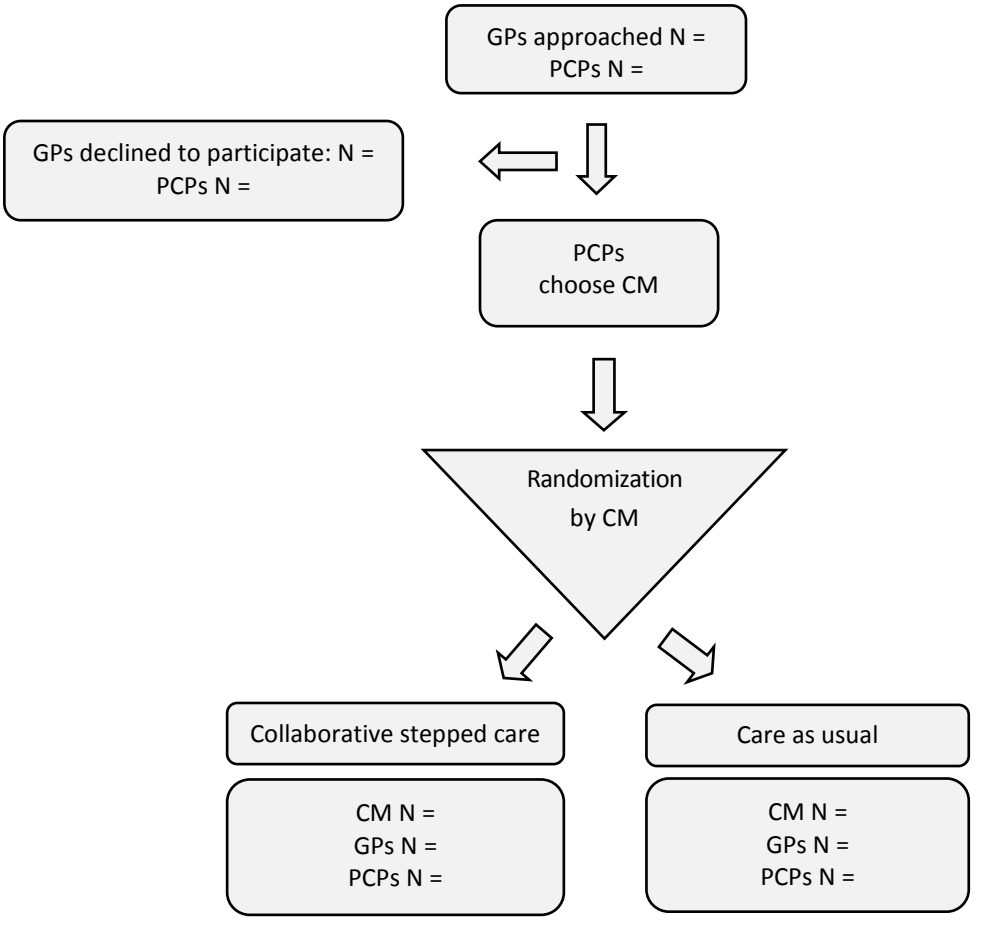

Figure 1. Flowchart showing the recruitment and randomisation of care managers and practices. GP: general practitioner, PCP: primary care practice, CM: care manager.

Recruitment of patients

Recruitment of patients will take place in two phases: a screening phase and a diagnostic phase. Patients will either be referred by their GP or will receive an invitation to participate based on a selection of the electronic medical record system

of the GP. Patients are blinded for randomisation status until they have returned the baseline questionnaire.

Screening phase

GPs are able to refer a patient by handing a patient an information letter, an informed consent form and a short screening instrument: the Patient Health Questionnaire anxiety subscale (PHQ22) (Spitzer *et al.* 1999). This measure has shown good psychometric properties for screening for anxiety disorders (Spitzer *et al.* 1999; Diez-Quevedo *et al.* 2001).

In cluster randomisation, when dependent on referrals of GPs, a known problem is the inclusion of patients in the CAU group (Farrin *et al.* 2005). To diminish recruitment bias, referral by GPs is complemented with selection on basis of screening in this study. A number of patients will be selected from the electronic medical records of the GPs according to the following criteria: they are older than 18 years of age and had contact with their GP in the past four months for one of the following reasons: psychological or social problems, muscle or skeletal pain, fatigue, hyperventilation, fainting, stomach ache, complaints about functioning of the heart or head ache. These patients will receive an information letter, an informed consent form and the PHQ-22. Of patients who return the PHQ-22 and give informed consent, the score on the PHQ-22 will be calculated. Patients will be considered screen-positive if they answer affirmatively to the screening questions of the PHQ22 and list at least 4 symptoms for panic or at least 1 symptom for general anxiety (Spitzer *et al.* 1999). For PD, threshold criteria will be used (Lowe *et al.* 2003), where as for GAD the sub threshold criteria will be used to increase sensitivity (Diez-Quevedo *et al.* 2001). Screen-positive patients will enter the diagnostic phase and will be contacted by telephone to perform a diagnostic interview.

Diagnostic phase

Diagnostic interviews will be conducted by trained research assistants who will be blind to the randomisation scheme. The MINI-PLUS International Neuropsychiatric Interview is a semi-structured interview that is often used for DSM-IV classification (Sheehan *et al.* 1998; van Vliet *et al.* 2000). Telephone administered psychiatric

interviews are found to have a high concordance with in-person interviews (Wells *et al.* 1988). The interviewers will have the opportunity to consult a psychiatrist, who is also blind to randomisation status, when they are uncertain of a diagnosis. Patients with a primary diagnosis of PD and/or GAD and who do not meet any of the exclusion criteria will receive a second information letter, baseline questionnaires and a second informed consent form. Patients will be offered the choice of a pen and paper version or an internet based version of the questionnaire. If the patient returns the baseline questionnaires and gives informed consent, the patient will be included in the study. Patients in the CSC group will be invited for a consultation with the care manager whereas patients in the CAU group will be advised to seek contact with their GP for treatment of their anxiety complaints. GPs in the control group will not be notified of the diagnosis of participating patients. Figure 2 shows a flowchart of participating patients.

Sample size

The aim of the trial is to detect a clinically relevant difference of 0.5 SD (Cohen's effect size) of CSC versus CAU on the continuous measure of the Beck Anxiety Inventory (BAI) (Cohen 1988). Sample size calculation is based on scores of 281 primary care patients in the multisite Netherlands Study of Depression and Anxiety (NESDA) (Penninx *et al.* 2008) with a diagnosis of PD or GAD in the last six months. The mean BAI score in this sample was 16.94, with an SD of 10.49 (range 0-58). Hence, the expected difference between CSC and CAU is 6 points on the BAI. To demonstrate this difference with alpha = 0.05 and a power of 0.90, 64 cases per arm are needed $((1.96 + 1.28)^2 * 10.49^2 * 2)/6^2)$. Since the average class size (n) is estimated to be 5 and the intraclass correlation coefficient (rho) is expected to be 0.01 (Adams *et al.* 2004; Gilbody *et al.* 2008), we apply an inflation factor of 1.04 (inflation factor = 1 + (n-1) x rho = 1 + 4 * 0.01 = 1.04) (Cosby *et al.* 2003). To be able to analyze 67 completers per arm and with an estimated 25% loss to follow-up, we aim to include 89 patients per arm.

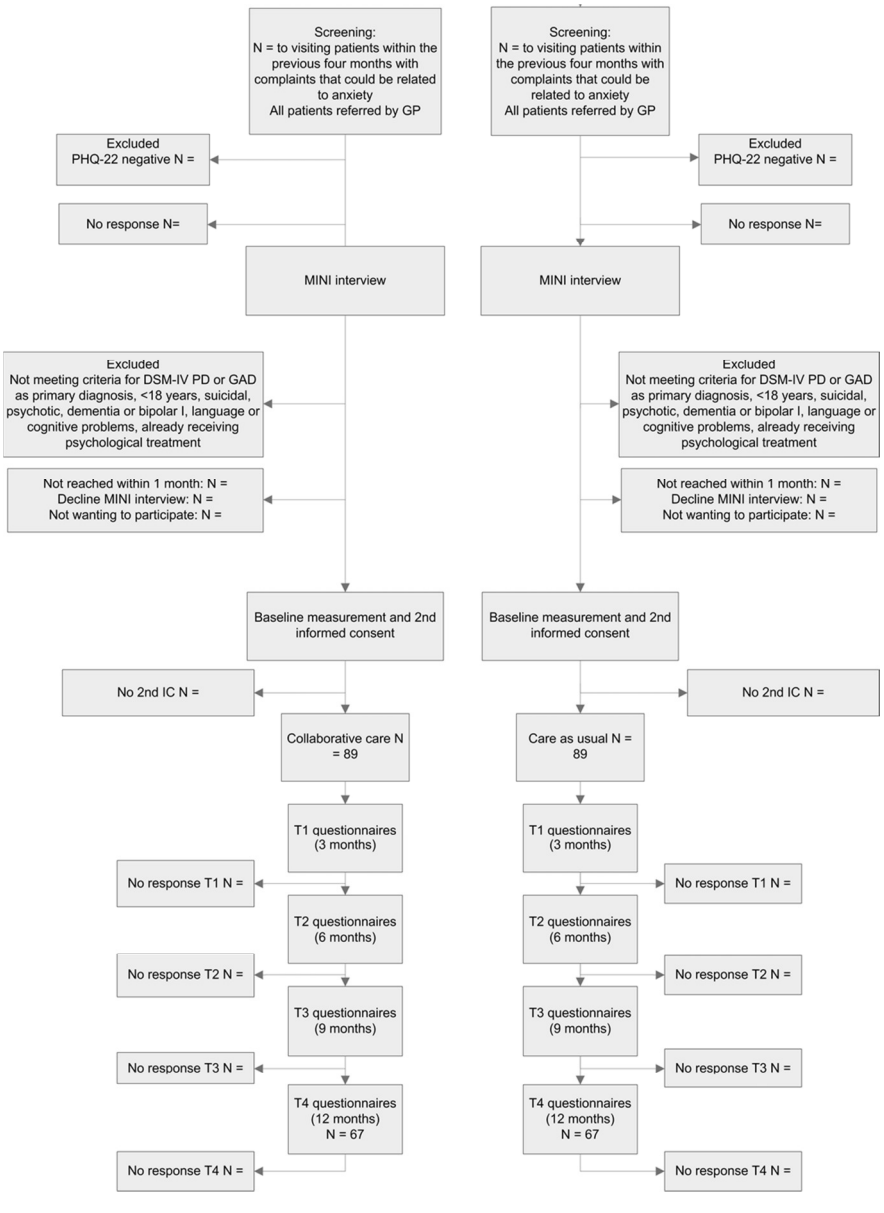

Figure 2. Flowchart of participants. GP: general practitioner, PCP: primary care practice, PHQ22: Patient Health Questionnaire anxiety sub-scale, MINI-interview: MINI-International Neuropsychiatric Interview.

Intervention

Training

Care managers randomised to the intervention group will receive three days of training in the nature of anxiety disorders, collaborative care, the guided self-help intervention and cognitive behavioural therapy (CBT). These training sessions will be conducted by a psychologist (AM), the psychiatrist who developed the guided self-help method (van Boeijen 2006) and two experienced cognitive behavioural therapists working at the regional mental health centre *Rivierduinen*.

GPs in the intervention group will receive three hours of training in the recognition of anxiety disorders, motivating patients for treatment, collaborative care and the medication algorithm. A psychiatrist (AvB), a GP (HvM) and a psychologist (AM) will provide this training.

Consultant psychiatrists will receive two hours of training in collaborative care, medication for PD and/or GAD and giving consultations in primary care. Two psychiatrists (AvB and CFC) and a psychologist (AM) will provide this training.

Treatment in the intervention group

1. Collaborative stepped care

In accordance with the collaborative care model, care is provided by a team of the GP, the care manager, the patient and a consultant psychiatrist. The collaborative stepped care intervention is composed of four steps:

1) Guided self-help
2) Cognitive behavioural therapy (CBT)
3) Antidepressants according to a medication algorithm
4) Optimisation of medication in primary care or referral to secondary care

After each step, progress is evaluated with the Beck Anxiety Inventory (BAI) (Beck et al. 1988a). The goal of the intervention is remission, according to the BAI score (See 7. Monitoring for remission criteria). If a patient does not achieve criteria for remission after concluding a step, he or she proceeds with the next step. For example, when a patient does not achieve criteria for remission concluding the guided self-help program (step 1), he or she is offered CBT treatment (step 2). In contrast, when a

patient does achieve remission after the guided self-help program, he or she enters a program of relapse prevention.
The care manager coordinates care, delivers guided self-help and CBT and evaluates each step. The GP prescribes medication and evaluates progress with the care manager. The care manager as well as the GP can consult a consultant psychiatrist about treatment decisions. The active phase of the treatment lasts for at least 12 weeks and has a maximum of 34 weeks. Patients' adherence to the program is enhanced by contracting and active monitoring. Relapse prevention is provided by the care manager through monthly follow-up calls, until twelve months after the beginning of treatment. Figure 3 depicts the treatment algorithm.

2. Contracting
When a patient is included in the study, he or she is invited for a first meeting with the care manager and GP. They briefly discuss the patients symptoms and explain the diagnosis. The patient is actively involved in the treatment plan by contracting. The patient receives a copy of the treatment plan.

3. Improving adherence
Premature termination of treatment and diminished adherence to treatment are associated with poorer outcomes. Therefore, patient adherence is encouraged by psycho-education, goal setting and by frequent follow-up appointments in which both adherence and progress are evaluated. Provider adherence to the treatment protocol is encouraged by instructions from the researchers and newsletters, by frequent reporting about the care given, by recording of sessions and by regular supervision. Care managers attend a supervision group led by a cognitive behavioural therapist every three weeks. They also have the opportunity to discuss problems and exchange experiences through an intranet forum.

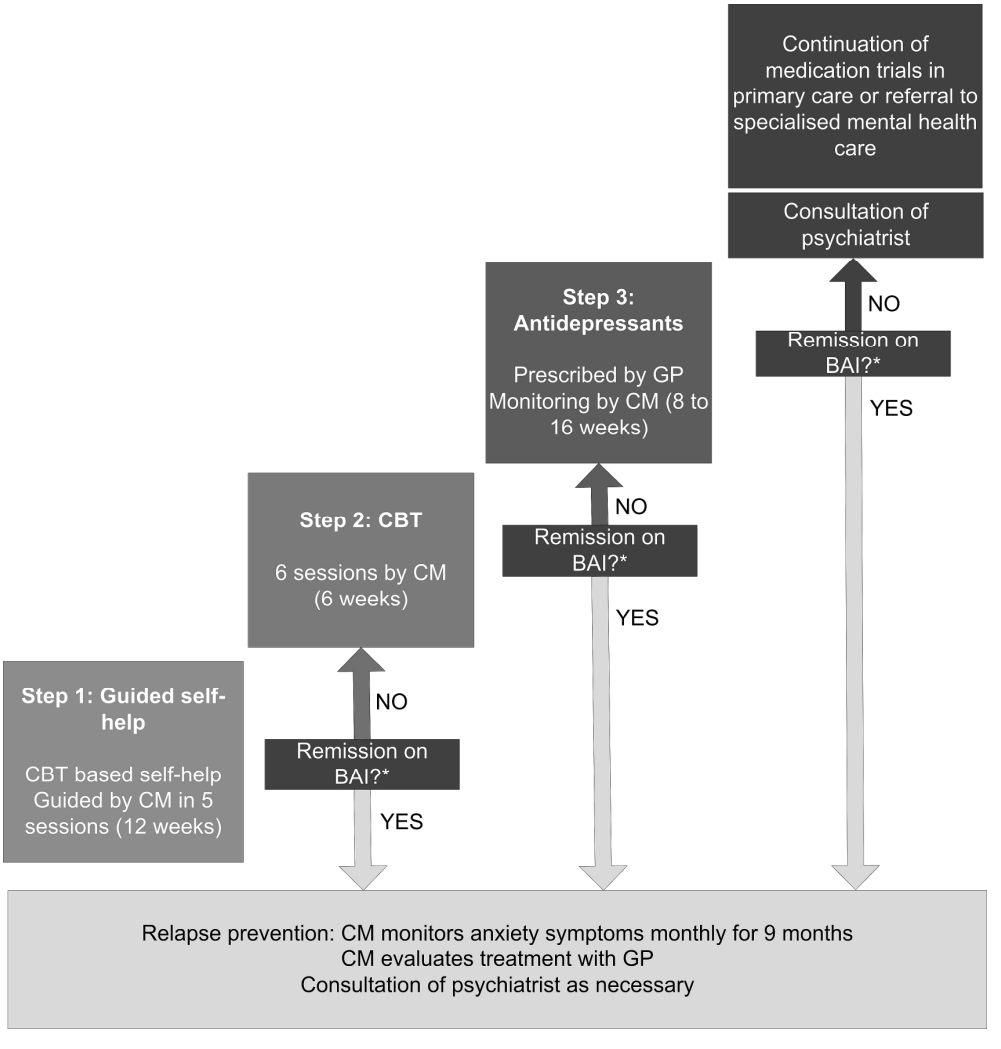

Figure 3. Treatment algorithm
**Remission is defined as a 50% reduction in score on the BAI plus a score of 11 or below. BAI = Beck Anxiety Inventory, CM = care manager, GP= general practitioner.*

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4. Guided self-help

Step one in the intervention is a guided self-help method based on cognitive behavioural principles (van Boeijen *et al.* 2005a). This intervention was proven effective in a randomised controlled trial with patients with PD and/or GAD (van Boeijen *et al.* 2005b). In twelve weeks, the patient works through a self-help manual with information about anxiety disorders, automatic thoughts, relaxation techniques and exposure in vivo (van Boeijen 2007). Every chapter contains exercises for the patients to perform. In five short consultations spread over twelve weeks, the care manager informs the patient about the content of the manual, reinforces achievements and motivates the patient to continue. In addition, the patient is encouraged to find a "helper", a friend or a relative, who can help him or her perform exercises and support the patient to adhere to the program.

5. Cognitive Behavioural Therapy (CBT)

CBT has been proven effective in numerous studies for both PD and GAD and is recommended as a first line treatment in international guidelines (van Balkom A.J.L.M. *et al.* 1995; Hunot *et al.* 2007). For this study, a short duration protocol was developed based on (inter)national guidelines and available manuals for the treatment of anxiety disorders with CBT (Clark 1989; Wells 1997; Otto & Deveney 2005).

A separate treatment protocol for PD and GAD is used, depending on the primary diagnosis of the patient. The CBT comprises a course of 6 sessions of 45 minutes provided by the care manager. All fundamental elements of CBT are represented in this protocol. For PD the main topics are psycho-education (e.g. the "cycle of panic"), registration of panic attacks, interoceptive exposure, recognition and modification of anxiety evoking automatic thoughts and behavioural experiments. The protocol for GAD focuses on psycho-education, recognition and modification of anxiety evoking automatic thoughts and meta-cognitions (Wells 2007). Both protocols employ homework assignments.

6. Medication

GPs are encouraged to adhere to an antidepressant algorithm to optimise the prescription of antidepressants. The choice of recommended antidepressants was

based on (inter)national guidelines. The algorithm includes time to titrate to daily dosages (2 weeks), time to respond (partially or remission, 4 weeks) and step-up criteria and methods (e.g. 'partial response: increase dose', 'no response: switch medication'). The care manager monitors adherence, adverse effects and response to treatment with the BAI. The GP and the care manager consult a psychiatrist when necessary. If the patient fulfils criteria for remission, medication treatment should be continued until twelve months after the initiation of medication treatment. If the patient does not respond or adhere to medication, the GP contacts the psychiatrist to discuss the options for further treatment. If further treatment in the primary care setting is not feasible, the patient may be referred to specialty mental health care.

7. Monitoring

The care manager monitors anxiety symptoms with the BAI (Beck *et al.* 1988). The goal of the intervention is remission, defined as a 50 percent reduction in score plus a score of 11 or below (see S*econdary outcome measures).* At the start of treatment the care manager administers the BAI and calculates a "target score" (remission) for each patient. The care manager then assesses the BAI at the end of step one and step two. During step three (medication), the care manager monitors symptoms more frequently: in week four and eight of medication use. If the patient switches medication this pattern is repeated.

8. Relapse prevention

If a patient achieves remission after step one, two or three, relapse prevention is offered by the care manager. The care manager calls the patient every month, to assess anxiety symptoms with the BAI. If the BAI score of a remitted patient increases to a score of 12 or above on two consecutive measurements, the care manager consults the psychiatrist about the next step to be taken. The patient can "step up" to the next step (i.e. step 2: CBT or step 3: medication) or be referred to specialty mental health care. Relapse prevention lasts until one year after starting treatment.

9. Referral to specialty mental health care

There can be several reasons for referring a patient to specialty mental health care: diagnostic uncertainty, complex psychosocial issues, poor response to treatment, patient preferences or emerging severe psychopathology. Referral to specialty mental health care is always discussed with the consultant psychiatrist.

Treatment in the control group

Half of the PCPs function as a control group. These GPs and care managers receive no training and they provide their usual care to their patients. There is a Dutch guideline available for all GPs about the treatment of anxiety disorders in primary care (Terluin *et al.* 2004). Care as usual comprises every form of care the GP is used to offer to his patient (e.g. watchful waiting, prescription of medication, referral to a mental health care professional or any other form of care the GP offers to his patient). The actual content of usual care will be assessed with the Scale for Medical Utilisation of Health Services (van der Feltz-Cornelis, 2002).

Data collection

Measurement will take place at baseline (T0), three (T1), six (T2), nine (T3) and twelve months (T4) after inclusion. The filled out pen and paper questionnaires will be processed anonymously by blinded research-assistants. The internet-questionnaires will be processed automatically.

Outcome parameters

1. Primary outcome measure

The severity of anxiety symptoms is measured with the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988a). This measure lists 21 symptoms of anxiety like feeling hot, scared or nervous. Patients are instructed to rate how much each of these symptoms bothered them in the past week, including today. Each item can be rated on a 4 point Likert scale, ranging from 0 (Not at all) to 3 (Severely) yielding a maximum total score of 63 points. The instrument has good psychometric properties (Ferguson 2000a).

2. Secondary outcome measure

Remission

As there is no standard "remission score" for the BAI, we calculated this score following the criteria of clinical significance of Jacobson & Truax (Jacobson & Truax 1991). These authors state that the best method to define recovery is to calculate the mean between the mean score of a population with the disorder and the mean score of a population without the disorder. We were able to derive these data of patients with or without PD or GAD from the NESDA study (Penninx *et al.* 2008), resulting in a score of 11. Because the BAI score is not a part of the diagnostic procedure, it is expected that not every patient will score 11 or higher on the BAI. Therefore, we added the element of a 50 percent reduction in score to the definition of remission. In sum, remission is defined as a score of 11 or below, plus a 50% reduction in score.

3. Additional outcome measures

Anxiety severity and impairment

Anxiety severity and impairment are measured by the Overall Anxiety Severity and Impairment Scale (OASIS) (Norman *et al.* 2006). This scale was developed to measure severity of anxiety and impairment caused by anxiety across different anxiety disorders and showed good reliability and validity (Campbell-Sills *et al.* 2008). The scale consists of five questions about frequency of anxiety, severity of anxiety, avoidance, interference with tasks and interference of social relationships. The scale was translated in Dutch according to the forward-backward translation method.

Physical symptoms

Physical symptoms are measured by the Physical Symptoms Questionnaire (LKV: Lichamelijke Klachten Vragenlijst (Hemert 2003)), which assesses the number and intensity of functional somatic complaints a patient is experiencing. The Whitely Index (dimensional version (Speckens *et al.* 1996a; Speckens *et al.* 1996b)) measures attitudes about diseases (hypochondriasis). As these symptoms often co-occur with anxiety disorders, it is interesting to see whether these symptoms also decrease when treating the anxiety disorder.

Quality of life

Quality of life is a measure that allows comparison in different studies and (mental and physical) disorders. In this study, quality of life is assessed with the EuroQol (EQ-5D) (Euroqol group 1995) and the Short Form-36 (SF-36) (Ware & Sherbourne 1992), both validated instruments for measuring general health-related quality of life. The EQ-5D descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels (no problems, some problems, and extreme problems), thus defining 243 (3^5) distinct health states. The SF-36 is an often used measure that assesses eight health concepts (Ware & Sherbourne 1992).

4. Effect modifiers

Demographic variables

The following demographic variables are measured at baseline: age, gender, nationality and ethnicity, marital status, living conditions, education and work status.

Physical illness

Co-morbid physical illness is measured at baseline by means of a questionnaire developed by Statistics Netherlands (the CBS list), which lists 28 chronic conditions (e.g. diabetes type II and vascular disease). Chronic medical illness is found to be related to more severe symptoms at baseline, but not to a different treatment response in the treatment of anxiety disorders (Roy-Byrne *et al.* 2005c).

Depressive symptoms

Depressive symptoms are assessed with the depression-subscale of the Patient Health Questionnaire (PHQ9) (Spitzer *et al.* 1999; Kroenke *et al.* 2001), a brief and valid instrument which measures each of the DSM-IV criteria for major depressive disorder. The total score gives an indication about the severity of depressive symptoms. Depression is related to more severe symptoms at baseline and after treatment, but not to a different treatment response (van Balkom *et al.* 2008). Depressive symptoms are assessed at all measurement points, to see whether

depressive symptoms also reside when treating the anxiety disorder and to be able to detect a possible difference between PD and GAD.

Coping

The use of specific coping styles is measured by the Utrecht Coping List (UCL: Utrechtse Coping Lijst) (Schreurs *et al.* 2007). This list assesses the frequency of using seven different coping styles: active coping, palliative reaction, avoidance, seeking social support, passive coping, expression of emotions and comforting thoughts. Coping styles are found to be related to outcome in mental disorders (Vollrath *et al.* 1996). There is a debate whether coping styles are sensitive to change following treatment.

Economic evaluation

The aim of this economic evaluation is to assess the cost-effectiveness and to estimate cost utility of CSC compared to CAU. This will be done by relating the difference in direct medical costs per patient receiving CSC or CAU to the difference in terms of reduction in score on the BAI (cost-effectiveness) and *quality adjusted life years (QALY)* gained (cost-utility). This will yield a cost per unit of the BAI and per QALY estimate. QALY's will be estimated using the 'Dutch EQ-5D tariff', which is used to calculate utilities for EQ-5D health states for the cost utility analyses of Dutch health care programs and treatments (Lamers *et al.* 2006). The analyses will also be performed including productivity costs.

Medical costs

For calculating the total direct medical costs, the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) (Hakkaart-van Roijen 2002; Hakkaart-van Roijen *et al.* 2006) is used. The Tic-P measures direct costs of medical treatment such as the number of contacts with the GP and multiple other care providers (e.g. medical specialists and paramedics) during the last three months. Medication use is measured during the last four weeks. The costs will be estimated in line with the Dutch guidelines for cost calculations in health care (Oostenbrink *et al.* 2004). Reference unit prices of the corresponding health care services will be applied,

and adjusted to the year of the study according to the consumer price index. Since the collaborative stepped care model is a new kind of intervention, a unit price per session is currently not available. To determine a reference price for this intervention a micro-costing study will be performed in at least three PCPs delivering the collaborative care intervention. Time for face-to-face contacts with the patient as well as indirect time per contact (e.g. mutual consultation contacts between GP and the care manager or the consultant psychiatrist) will be measured. For reasons of comparison the costs for a GP contact in the CAU study-arm will be measured applying a similar micro-costing methodology.

Productivity costs

For collecting data on productivity losses a short form of the Health and Labour questionnaire (SF-HQL) (van Roijen *et al.* 1996) is used. The SF-HLQ consists of three modules that measure productivity losses: absence from work, reduced efficiency at work and difficulties with job performance (van Dam *et al.* 1998).

Productivity losses as measured by the SF-HQL are valued according to the average value added per worker by age and gender per day and per hour. If respondents indicate that they have been absent for the entire recall period, data will be collected from the time when the period of long-term absence started. This additional information will be used to value the production losses according to the "friction cost method" (Koopmanschap *et al.* 1995). This method takes into account the economic circumstances that limit the losses of productivity to society, which are related to the fact that a formerly unemployed person may replace a person who becomes disabled.

Statistical analyses

Intention-to-treat analysis will be performed by multilevel analysis with time as the first hierarchical level, patients as the second hierarchical level and care managers with their PCPs in the third level (Twisk 2006). Possible confounding characteristics (e.g. age, gender or level of experience) will be included in the analysis models. Propensity scores will be used to correct for bias that could be introduced by selection bias. In this calculation, variables that are not considered as dependent variables or confounders of interest are used to predict the chance that a patient is included in

either the CSC or the CAU group, using logistic regression analysis. This can be considered an appropriate procedure for cluster randomised trials (Van der Feltz-Cornelis *et al.* 2006).
Direct and indirect costs of the interventions will be reported. The results of the cost and QALY analyses will be presented as mean values with standard errors. Cost-effectiveness and cost-utility analyses will be presented in incremental cost-effectiveness ratios. The uncertainty will be assessed using bootstrapping (van Hout *et al.* 1994) and acceptability curves will be presented. As principled methods (e.g. multiple imputation) take into account the special characteristics of cost data that affect their analysis, a principled method for dealing with missing data will be applied to our economic evaluation (Oostenbrink *et al.* 2003).

Ethical principles

The study protocol has been approved by the Medical Ethical Committee of the VU University Medical Centre at April 29, 2008 and by the Medical Ethics Committee of the Leiden University Medical Centre at October 2nd 2008.

Funding

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Discussion

The presumed poor quality of care in the primary care setting for such prevalent, disabling and costly disorders as PD and GAD set the basis for this study. The aims of this study are to improve the quality of care for these patients with an acceptable increase in costs.

This study is the first in which a stepped care approach is incorporated in a collaborative care intervention for the treatment of anxiety disorders in primary care. It is also the first study, to our knowledge, that evaluates the cost-effectiveness of such an intervention outside the United States. Effective elements of other studies have been brought together in the protocol of this study.

A strength of this study is its pragmatic design. There is a minimum of exclusion criteria. Furthermore, care is provided by health care professionals from the field, unlike in other studies evaluating collaborative care (Roy-Byrne *et al.* 2001; Rollman *et al.* 2005; Roy-Byrne *et al.* 2005b). Consequently, the results of this study may be generalised to naturalistic health care settings with a comparable primary health care system and will be easy to implement into practice.

REFERENCES

2001, Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).

Adams, G., Gulliford, M. C., Ukoumunne, O. C., Eldridge, S., Chinn, S. & Campbell, M. J. (2004). Patterns of intra-cluster correlation from primary care research to inform study design and analysis. J Clin Epidemiol. **57**, 785-794.

Alonso, J., Buron, A., Bruffaerts, R., He, Y., Posada-Villa, J., Lepine, J. P., Angermeyer, M. C., Levinson, D., De Girolamo, G., Tachimori, H., Mneimneh, Z. N., Medina-Mora, M. E., Ormel, J., Scott, K. M., Gureje, O., Haro, J. M., Gluzman, S., Lee, S., Vilagut, G., Kessler, R. C. & Von Korff, M. (2008). Association of perceived stigma and mood and anxiety disorders: results from the World Mental Health Surveys. Acta Psychiatr Scand. **118**, 305-314.

Andlin-Sobocki, P. & Wittchen, H. U. (2005). Cost of anxiety disorders in Europe. Eur J Neurol. **12 Suppl 1**, 39-44.

Andrews, G., Oakley-Browne, M., Castle, D., Judd, F. & Baillie, A. (2003). Summary of guideline for the treatment of panic disorder and agoraphobia. *Australasian Psychiatry* **11**, 29-33.

Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* **56**, 893-897.

Bower, P., Gilbody, S., Richards, D., Fletcher, J. & Sutton, A. (2006). Collaborative care for depression in primary care: Making sense of a complex intervention: systematic review and meta-regression. *Br.J.Psychiatry* **189**, 484-493.

Buist-Bouwman, M. A., de Graaf, R., Vollebergh, W. A., Alonso, J., Bruffaerts, R. & Ormel, J. (2006). Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta psychiatrica Scandinavica* **113 (6)**, 492-500.

Campbell-Sills, L., Norman, S. B., Craske, M. G., Sullivan, G., Lang, A. J., Chavira, D. A., Bystritsky, A., Sherbourne, C., Roy-Byrne, P. & Stein, M. B. (2008). Validation of a brief measure of anxiety-related severity and impairment: The Overall Anxiety Severity and Impairment Scale (OASIS). *J Affect.Disord.*

Clark, D. M. Anxiety states: Panic and generalized anxiety. Hawton, K., Salkovskis, P. M., and Clark, D. M. Eds. Cognitive behaviour therapy for psychiatric problems: A practical guide. 52-96. 1989. Oxford, Oxford University Press.

Cohen, J. (1988). Statistical power analysis for the behavioral science. Second Edition. Lawrence Erlbaum Associates,Inc.: Hillsdale.

Cosby, R. H., Howard, M., Kaczorowski, J., Willan, A. R. & Sellors, J. W. (2003). Randomizing patients by family practice: sample size estimation, intracluster correlation and data analysis. Fam.Pract. **20**, 77-82.

Cramer, V., Torgersen, S. & Kringlen, E. (2005). Quality of life and anxiety disorders: a population study. J Nerv Ment Dis **193**, 196-202.

de Jong, S. J., van Steenbergen-Weijenburg, K. M., Huijbregts, K. M., Vlasveld, M., Marwijk, H. W. J., Beekman, A. & van der Feltz-Cornelis C.M. (2009). The depression initiative. Description of a collaborative care model for depression and of the factors influencing

its implementation in the primary care setting in the Netherlands. *International Journal of Integrated Care* **9**.

Diez-Quevedo, C., Rangil, T., Sanchez-Planell, L., Kroenke, K. & Spitzer, R. L. (2001). Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients. *Psychosom.Med* **63**, 679-686.

Euroqol group (1995). *Eq-5D user guide*. Sanders instituut, EUR: Rotterdam.

Farrin, A., Russell, I., Torgerson, D. & Underwood, M. (2005). Differential recruitment in a cluster randomized trial in primary care: the experience of the UK back pain, exercise, active management and manipulation (UK BEAM) feasibility study. *Clin.Trials* **2**, 119-124.

Ferguson, R. J. Using the Beck Anxiety Inventory in Primary Care. Maruish, M. E. Handbook of psychological assessments in primary care settings. 509-535. 2000. Mahwah, NJ, Lawrence Erlbaum.

Fernandez, A., Haro, J. M., Martinez-Alonso, M., Demyttenaere, K., Brugha, T. S., Autonell, J., De Girolamo, G., Bernert, S., Lepine, J. P. & Alonso, J. (2007). Treatment adequacy for anxiety and depressive disorders in six European countries. *Br J Psychiatry* **190**, 172-173.

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch.Intern.Med.* **166**, 2314-2321.

Gilbody, S., Bower, P., Torgerson, D. & Richards, D. (2008). Cluster randomized trials produced similar results to individually randomized trials in a meta-analysis of enhanced care for depression. *J Clin Epidemiol.* **61**, 160-168.

Gorman, J. M. (2003). Treating generalized anxiety disorder. *J Clin Psychiatry* **64 Suppl 2**, 24-29.

Hakkaart-van Roijen, L. (2002). Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in Dutch). Institute for Medical Technology Assessment: Rotterdam.

Hakkaart-van Roijen, L., van Straten, A., Al, M., Rutten, F. & Donker, M. (2006). Cost-utility of brief psychological treatment for depression and anxiety. Br J Psychiatry **188**, 323-329.

Hemert, A. M. (2003). Lichamelijke Klachten Vragenlijst. Leids Universitair Medisch Centrum: Leiden.

Hunot, V., Churchill, R., Silva, d. L. & Teixeira, V. (2007). Psychological therapies for generalised anxiety disorder. *Cochrane Database Syst.Rev*, CD001848.

Jackson, J. L., Passamonti, M. & Kroenke, K. (2007). Outcome and impact of mental disorders in primary care at 5 years. *Psychosom Med* **69**, 270-276.

Jacobson, N. S. & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* **59**, 12-19.

Katon, W., Russo, J., Sherbourne, C., Stein, M. B., Craske, M., Fan, M. Y. & Roy-Byrne, P. (2006). Incremental cost-effectiveness of a collaborative care intervention for panic disorder. *Psychol.Med* **36**, 353-363.

Katon, W., Von Korff, M., Lin, E., Unutzer, J., Simon, G., Walker, E., Ludman, E. & Bush, T. (1997). Population-based care of depression: effective disease management strategies to decrease prevalence. *Gen.Hosp.Psychiatry* **19**, 169-178.

Katon, W., Von, K. M., Lin, E. & Simon, G. (2001). Rethinking practitioner roles in chronic illness: the specialist, primary care physician, and the practice nurse. *Gen.Hosp.Psychiatry* **23**, 138-144.

Katon, W. J., Roy-Byrne, P., Russo, J. & Cowley, D. (2002). Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. *Arch.Gen.Psychiatry* **59**, 1098-1104.

Kessler, R. C., Greenberg, P. E., Mickelson, K. D., Meneades, L. M. & Wang, P. S. (2001). The effects of chronic medical conditions on work loss and work cutback. *J Occup.Environ.Med* **43**, 218-225.

Koopmanschap, M. A., Rutten, F. F., van Ineveld, B. M. & van Roijen, L. (1995). The friction cost method for measuring indirect costs of disease. *J Health Econ.* **14**, 171-189.

Kroenke, K., Spitzer, R. L. & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J.Gen.Intern.Med.* **16**, 606-613.

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O. & Lowe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann.Intern.Med* **146**, 317-325.

Lamers, L. M., McDonnell, J. & Stalmeier, P. F. (2006). The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ* **15**, 1121-1132.

Lieb, R., Becker, E. & Altamura, C. (2005). The epidemiology of generalized anxiety disorder in Europe. *Eur Neuropsychopharmacol.* **15**, 445-452.

Lowe, B., Grafe, K., Zipfel, S., Spitzer, R. L., Herrmann-Lingen, C., Witte, S. & Herzog, W. (2003). Detecting panic disorder in medical and psychosomatic outpatients: comparative validation of the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire, a screening question, and physicians' diagnosis. *J Psychosom.Res* **55**, 515-519.

Mathias, S. D., Fifer, S. K., Mazonson, P. D., Lubeck, D. P., Buesching, D. P. & Patrick, D. L. (1994). Necessary but not sufficient: the effect of screening and feedback on outcomes of primary care patients with untreated anxiety. *J Gen Intern Med* **9**, 606-615.

Mechanic, D. (2007). Barriers to help-seeking, detection, and adequate treatment for anxiety and mood disorders: implications for health care policy. *J Clin Psychiatry* **68 Suppl 2**, 20-26.

NHG. NHG Standaard Angststoornis [Dutch college of general practitioners, Practical guideline Anxiety disorder]. 2004. Retrieved March 2, 2007, from Nederlands Huisartsen Genootschap (NHG). Website: http://nhg.artsennet.nl/upload/104/standaarden/M62/start.htm.

Norman, S. B., Cissell, S. H., Means-Christensen, A. J. & Stein, M. B. (2006). Development and validation of an Overall Anxiety Severity And Impairment Scale (OASIS). *Depress.Anxiety* **23**, 245-249.

Nutting, P. A., Rost, K., Smith, J., Werner, J. J. & Elliot, C. (2000). Competing demands from physical problems: effect on initiating and completing depression care over 6 months. *Arch.Fam.Med.* **9**, 1059-1064.

Oostenbrink, J. B., Al, M. J. & Rutten-van Molken, M. P. (2003). Methods to analyse cost data of patients who withdraw in a clinical trial setting. *Pharmacoeconomics.* **21**, 1103-1112.

Oostenbrink, J. B., Bouwmans, C. A. M., Koopmanschap, M. A., & et al. (2004). *Handleiding voor kostenonderzoek, methoden en standaardkostprijzen voor economische evaluaties in de gezondheidszorg (Manual for Research on Costs, Methods and Standardized Cost Prices for Economic Evaluation in Health Care).* Health Care Insurance Board (College voor zorgverzekeringen):

Ormel, J., Koeter, M. W., Brink, W. v. d. & Willige, G. v. d. (1991). Recognition, management, and course of anxiety and depression in general practice. *Archives of General Psychiatry* **48**, 700-706.

Otto, M. W. & Deveney, C. (2005). Cognitive-behavioral therapy and the treatment of panic disorder: efficacy and strategies. *J Clin Psychiatry* **66 Suppl 4**, 28-32.

Penninx, B. W., Beekman, A. T., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P., Cuijpers, P., De Jong, P. J., Van Marwijk, H. W., Assendelft, W. J., Van Der, M. K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W. J., Ormel, J. & van Dyck, R. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* **17**, 121-140.

Prins, M. A., Verhaak, P. F., Bensing, J. M. & Van Der, M. K. (2008). Health beliefs and perceived need for mental health care of anxiety and depression--the patients' perspective explored. *Clin Psychol Rev* **28**, 1038-1058.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.

Rollman, B. L., Hanusa, B. H., Lowe, H. J., Gilbert, T., Kapoor, W. N. & Schulberg, H. C. (2002). A randomized trial using computerized decision support to improve treatment of major depression in primary care. *J Gen Intern Med* **17**, 493-503.

Roy-Byrne, P. P., Wagner, A. W. & Schraufnagel, T. J. (2005a). Understanding and treating panic disorder in the primary care setting. *J Clin Psychiatry* **66 Suppl 4**, 16-22.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005b). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.

Roy-Byrne, P., Stein, M. B., Russo, J., Craske, M., Katon, W., Sullivan, G. & Sherbourne, C. (2005c). Medical illness and response to treatment in primary care panic disorder. *Gen.Hosp.Psychiatry* **27**, 237-243.

Roy-Byrne, P. P. & Wagner, A. (2004). Primary care perspectives on generalized anxiety disorder. *J Clin Psychiatry* **65 Suppl 13**, 20-26.

Roy-Byrne, P. P., Katon, W., Cowley, D. S. & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* **58**, 869-876.

Schreurs, P. J. G., van de Willige, G., Brosschot, J. F., Tellegen, J. F., & Grauw, G. M. H. Handleiding Utrechtse Copinglijst UCL *[Utrecht Coping Questionnaire]*. 1 **22**, 288-274. 18-8-2007. Human Reproduction.

Schulberg, H. C., Block, M. R., Madonia, M. J., Scott, C. P., Lave, J. R., Rodriguez, E. & Coulehan, J. L. (1997). The 'usual care' of major depression in primary care practice. *Arch Fam Med* **6**, 334-339.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R. & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J.Clin.Psychiatry* **59 Suppl 20**, 22-33.

Smolders, M., Laurant, M., Roberge, P., Van Balkom, A., Van Rijswijk, E., Bower, P. & Grol, R. (2008). Knowledge transfer and improvement of primary and ambulatory care for patients with anxiety. *Can J Psychiatry* **53**, 277-293.

Speckens, A. E., Spinhoven, P., Sloekers, P. P., Bolk, J. H. & van Hemert, A. M. (1996a). A validation study of the Whitely Index, the Illness Attitude Scales, and the Somatosensory Amplification Scale in general medical and general practice patients. *J Psychosom.Res* **40**, 95-104.

Speckens, A. E., Van Hemert, A. M., Spinhoven, P. & Bolk, J. H. (1996b). The diagnostic and prognostic significance of the Whitely Index, the Illness Attitude Scales and the Somatosensory Amplification Scale. *Psychol.Med.* **26**, 1085-1090.

Spitzer, R. L., Kroenke, K. & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* **282**, 1737-1744.

Stein, M. B., Sherbourne, C. D., Craske, M. G., Means-Christensen, A., Bystritsky, A., Katon, W., Sullivan, G. & Roy-Byrne, P. P. (2004). Quality of care for primary care patients with anxiety disorders. *Am J Psychiatry* **161**, 2230-2237.

Terluin, B., Van heest, F. B., Van der Meer, K., Neomagus, G. J. H., Hekman, J., Aulbers, L. P. J., Starreveld, J. S. & Grol, M. H. (2004). NHG-Standaard Angststoornissen. *Huisarts en Wetenschap* **47**, 26-37.

The National Institute for Health and Clinical Excellence (NICE). CG22 Anxiety: Quick reference guide (amended) (2007, December 3). Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. Clinical guideline 22 (amended). Issue date: December 2004, with amendments. Website: http://www.nice.org.uk/nicemedia/pdf/CG022quickrefguideamended.pdf.

Twisk, J. W. R. (2006). *Applied Multilevel Analysis*. Cambridge University Press: Cambridge.

van Balkom A.J.L.M., Nauta, C. M. E. & Bakker, A. (1995). Metaanalyses on the treatment of panic disorder with agoraphobia: Review and reexamination. Clinical Psychology and Psychotherapy. 2, 1-14.

van Balkom, A. J., van Boeijen, C. A., Boeke, A. J., van Oppen, P., Kempe, P. T. & van Dyck, R. (2008). Comorbid depression, but not comorbid anxiety disorders, predicts poor outcome in anxiety disorders. *Depress.Anxiety* **25**, 408-415.

van Boeijen, C. A. (2006) Feasibility and efficacy of treatment for anxiety in primary care. Dissertation. Amsterdam, VU University.

van Boeijen, C. A. (2007) Handboek Begeleide Zelfhulp: Overwinnen van angstklachten *(Handbook guided self help: Overcoming anxiety).* Apeldoorn.

van Boeijen, C. A., van Balkom, A. J., van Oppen, P., Blankenstein, N., Cherpanath, A. & van Dyck, R. (2005a). Efficacy of self-help manuals for anxiety disorders in primary care: a systematic review. *Fam.Pract.* **22**, 192-196.

van Boeijen, C. A., van Oppen, P., van Balkom, A. J., Visser, S., Kempe, P. T., Blankenstein, N. & van Dyck, R. (2005b). Treatment of anxiety disorders in primary care practice: a randomised controlled trial. *Br J Gen Pract.* **55**, 763-769.

van Dam, Q. D., Spijker, A., Arends, L. R., Hakkaart-van Roijen, L., Donker.M.C.H. & Trijsburg, R.W. (1998). Costeffectiveness of psychotherapy: A feasiblity study (in Dutch). *J Pychotherapy* **24**, 5-22.

van der Feltz-Cornelis C.M. (2002). Psychiatric consultation for patients with somatoform disorder in general practice. Dissertation. Amsterdam, VU University.

Van der Feltz-Cornelis, C. M. & Ader, H. J. (2000). Randomization in psychiatric intervention research in the general practice setting. International Journal of Methods in Psychiatric Research **9**, 134-142.

Van der Feltz-Cornelis, C. M., van Oppen, P., Adèr, H. & van Dyck, R. (2006). Randomised Controlled Trial of a Collaborative Care Model with Psychiatric Consultation for Persistent Medically Unexplained Symptoms in General Practice. Psychother.Psychosom. **75**, 282-289.

van Hout, B. A., Al, M. J., Gordon, G. S. & Rutten, F. F. (1994). Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ.* **3**, 309-319.

van Roijen, L., Essink-Bot, M. L., Koopmanschap, M. A. & et al. (1996). Labor and health status in economic evaluation of health care. The Health and Labor Questionnaire. *Int J Technol Assess Health Care* **12**, 405-415.

van Vliet, I. M., Leroy, H., & van Megen, H. J. M. (2000). De MINI-Internationaal neuropsychiatrisch interview: een kort gestructureerd diagnostisch interview voor DSM-IV en ICD-10 psychiatrische stoornissen.LUMC: Leiden.

Vollrath, M., Alnaes, R. & Torgersen, S. (1996). Differential effects of coping in mental disorders: a prospective study in psychiatric outpatients. *J Clin Psychol.* **52**, 125-135.

Wagner, E. H., Austin, B. T. & Von, K. M. (1996). Organizing care for patients with chronic illness. *Milbank Q* **74**, 511-544.

Ware, J. E. & Sherbourne, C. D. (1992). The MOS 36-Item Short-Form Health Survey (SF-36). *Medical Care* **30**, 473-483.

Weiller, E., Bisserbe, J. C., Maier, W. & Lecrubier, Y. (1998). Prevalence and recognition of anxiety syndromes in five European primary care settings. A report from the WHO study on Psychological Problems in General Health Care. *Br J Psychiatry Suppl*, 18-23.

Wells, A. (1997). *Cognitive therapy of anxiety disorders: A practice manual and conceptual guide*. John Wiley & Sons Inc.: Hoboken.

Wells, A. (2007). Cognition about cognition: Metacognitive therapy and change in generalized anxiety disorder and social phobia. *Cognitive and Behavioral Practice* **14**, 18-25.

Wells, K. B., Burnam, M. A., Leake, B. & Robins, L. N. (1988). Agreement between face-to-face and telephone-administered versions of the depression section of the NIMH Diagnostic Interview Schedule. *J Psychiatr.Res* **22**, 207-220.

Wittchen, H. U. & Hoyer, J. (2001). Generalized anxiety disorder: nature and course. *J Clin Psychiatry* **62 Suppl 11**, 15-19.

Wittchen, H. U., Kessler, R. C., Beesdo, K., Krause, P., Hofler, M. & Hoyer, J. (2002). Generalized anxiety and depression in primary care: prevalence, recognition, and management. *J Clin Psychiatry* **63 Suppl 8**, 24-34.

Yonkers, K. A., Bruce, S. E., Dyck, I. R. & Keller, M. B. (2003). Chronicity, relapse, and illness--course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress.Anxiety* **17**, 173-179.

Young, A. S., Klap, R., Sherbourne, C. D. & Wells, K. B. (2001). The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry* **58**, 55-61.

Chapter 3

Study b

Effectiveness of collaborative stepped care for anxiety disorders in primary care: a pragmatic cluster randomised controlled trial

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Abstract

Objective To evaluate the effectiveness of collaborative stepped care compared to care as usual for adults with panic disorder or generalised anxiety disorder in primary care.

Design A cluster randomised controlled trial, with follow-up assessments at three, six, nine and twelve months.

Setting Forty-three primary care practices employing 63 general practitioners (GPs) and 31 mental health professionals in the Netherlands. The mental health professionals were randomised to deliver collaborative stepped care (16 mental health professionals, 23 practices) or care as usual (15 mental health professionals, 20 practices).

Participants An initial selection of 207 patients selected by their GP and 2499 patients selected from the electronic medical records resulted in 180 included patients with a DSM-IV diagnosis of panic disorder or generalised anxiety disorder. Mean age was 46.5 years (SD 15.5), the majority was female (68.3 %) and 91% completed at least one follow-up questionnaire.

Interventions One hundred fourteen patients received collaborative stepped care provided by a mental health professional (care manager), GP and a consultant psychiatrist who were trained in the collaborative stepped care intervention of three steps: guided self-help, cognitive behavioural therapy and antidepressants. Sixty-six patients received care as usual provided by their GP.

Main outcome measure Change in Beck Anxiety Inventory (BAI) score.

Results Collaborative stepped care was superior to care as usual at all follow-up measurements (difference in change scores 3 months -5.11, 95% confidence interval [CI] -8.28 to -1.94; 6 months -4.65, CI -7.93 to -1.38; 9 months -5.67, CI -8.97 to -2.36; 12 months -6.84, CI -10.13 to -3.55). Effect sizes of between-group differences were small to moderate.

Conclusions Collaborative stepped care, with guided self-help as a first step, was more effective than care as usual for primary care patients with panic disorder or generalised anxiety disorder.

Trial registration: Netherlands Trial Register NTR1071

Introduction

Panic disorder (PD) and generalised anxiety disorder (GAD) are two of the most disabling and costly anxiety disorders (Greenberg *et al.* 1999; Andlin-Sobocki & Wittchen 2005; Olatunji *et al.* 2007) that are frequently presented in primary care (Roy-Byrne & Wagner 2004; Roy-Byrne *et al.* 2005a). Both disorders often run a chronic course, since almost two thirds of the patients with one of these disorders still suffers from the disorder five years later (Yonkers *et al.* 2003). The majority of patients with PD or GAD receives general primary care (Bijl & Ravelli 2000; Stein *et al.* 2004). However, treatment offered in this setting often lacks adequate provision of psychotherapy or pharmacotherapy (Stein *et al.* 2011; Richards & Borglin 2011) as well as structural monitoring and relapse prevention.

To improve primary care treatment for these patients, collaborative care models have been developed. Collaborative care aims at supporting the general practitioner (GP) in providing evidence based, continuous care by bringing mental health expertise in the primary care team. A few studies provide evidence that collaborative care is more effective than usual primary care for patients with PD or GAD (Roy-Byrne *et al.* 2001; Rollman *et al.* 2005; Roy-Byrne *et al.* 2005b; Roy-Byrne *et al.* 2010). In these studies, the GP is supported by a consultant psychiatrist and/or a trained "care manager", often a (psychiatric) nurse or a psychologist, who monitors the patient's symptoms and provides systematic follow-up. The interventions included in collaborative care studies vary in complexity. For example, in an early study of Roy-Byrne and colleagues, the intervention consisted of psycho-education in combination with medication provided by a consultant psychiatrist (Roy-Byrne *et al.* 2001). In a recent large trial of Roy-Byrne and colleagues (2010) treatment consisted of an extensive program of computer supported cognitive behavioural therapy (CBT) provided by a care manager who was supervised by a psychiatrist and/or antidepressants prescribed by the GP. The intervention addressed four anxiety disorders (PD, GAD, social phobia and post traumatic stress disorder). The results of the collaborative care studies for anxiety disorders are indeed promising for improving care, at least in the United States. Research on collaborative care for depression has already shown that collaborative care may also improve care in other countries as well (Gilbody *et al.* 2006; Thota *et al.*

2012; Huijbregts *et al.* 2012). However, none of the previous collaborative care studies focusing on anxiety followed a stepped care approach, which is nowadays recommended in several national guidelines (Spijker *et al.* 2010; Kendall *et al.* 2011). Stepped care starts with the least intrusive, most effective intervention. The rationale behind stepped care is that it should enhance self-management and lead to an efficient use of resources (Bower & Gilbody 2005). The updated guideline of the National Institute of Clinical Excellence (NICE) in the UK includes a stepped care algorithm for GAD and PD, starting with a (low intensity) psychological intervention (National Institute for Health and Clinical Excellence 2011). However, evidence of the effectiveness of stepped care for anxiety disorders is not yet established firmly (Bower & Gilbody 2005; Seekles *et al.* 2011; Coull & Morris 2011).

To evaluate the effectiveness of collaborative stepped care, we designed a collaborative stepped care model. We incorporated three interventions based on former research in the primary care setting: guided self-help (van Boeijen *et al.* 2005) as a first step, followed by CBT and antidepressants according to a guideline based algorithm (van der Feltz-Cornelis CM *et al.* 2006). A care manager working in the primary care practice provides guided self-help, CBT and follow-up, monitors symptoms and adjusts treatment accordingly in consultation with the GP, who prescribes medication. A consultant psychiatrist is available for advice. We evaluated the effects of this model compared to care as usual using a pragmatic cluster randomised controlled trial to ensure a naturalistic treatment setting.

Methods

Objective

To evaluate the effectiveness of collaborative stepped care versus care as usual on the anxiety symptoms of adult primary care patients with a DSM IV diagnosis of panic disorder or generalised anxiety disorder.

Design

The study was a two armed, cluster randomised controlled trial. Unit of randomisation (clusters) were the mental health professionals who provided their services to the participating primary care practices.

Randomisation of clusters

All mental health professionals who provided their services to primary care practices located in the western part of the Netherlands (Leiden region) who were willing to participate in the study were eligible for participation. The participating mental health professionals were 28 psychiatric nurses and 3 primary care psychologists who provided their services to 43 primary care practices (with 63 participating physicians) in the Netherlands. The 31 mental health professionals were randomised using sequences obtained with an automated random sequence generation algorithm following a blocking scheme of variable length with allowance for restricted unbalance of at most three by an independent statistician. Sixteen mental health professionals serving 23 practices were allocated to the intervention group and 15 mental health professionals serving 20 practices were allocated to the control group (See Figure 1). Mental health professionals and general practitioners (GPs) were not blind to group assignment after randomisation. The design and methods of this study have been extensively described in our study protocol (Muntingh *et al.* 2009).

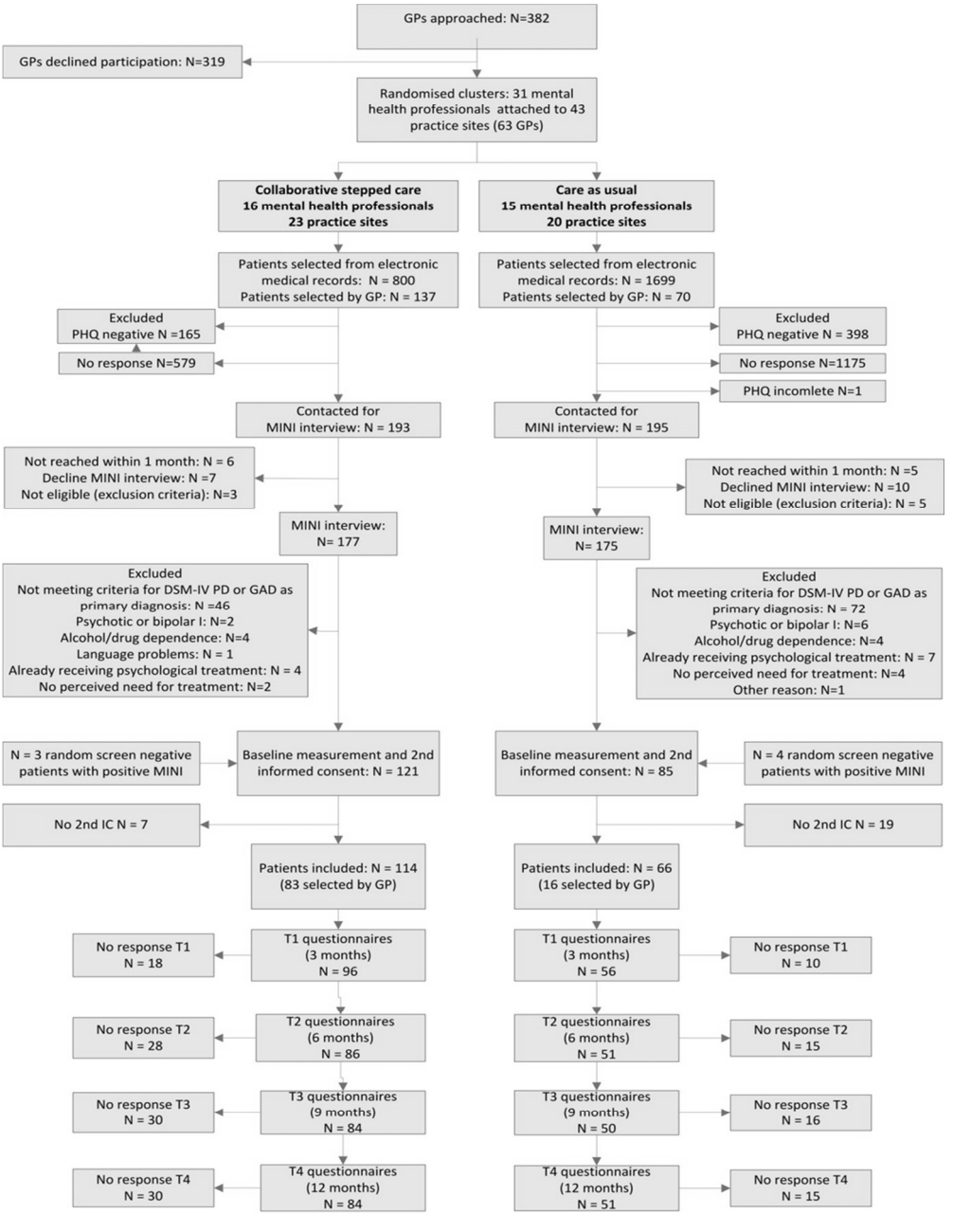

Figure 1. Flowchart of clusters and participants. GP: General practitioner, PHQ: Patient Health Questionnaire (anxiety modules), MINI-interview: MINI-International Neuropsychiatric Interview.

Patients

Inclusion criteria

Adult (>18 years of age) primary care patients with a primary diagnosis of panic disorder (PD) with or without agoraphobia and/or generalised anxiety disorder (GAD).

Exclusion criteria

Suicidal ideation, dementia or other severe cognitive disorders, psychotic disorder, bipolar disorder, dependence on drugs or alcohol, an unstable severe medical condition, insufficient knowledge of the Dutch language to complete the questionnaires, or receiving psychiatric or psychological treatment (>2 contacts per month). Receiving antidepressant medication was no reason for exclusion.

Recruitment

Between September 1st 2008 and March 31st 2010 patients were enrolled. GPs selected patients they encountered with anxiety problems for the study. In addition, a research assistant selected patients from the electronic medical records (EMR) who consulted the GP in the past four months for psychological or social problems, or physical symptoms possibly related to anxiety disorders (Kroenke *et al.* 1994; Roy-Byrne *et al.* 2008; Muntingh *et al.* 2009). Patients who gave informed consent completed a screening questionnaire: the Patient Health Questionnaire anxiety modules (Spitzer *et al.* 1999).

An independent trained research assistant, who was blind for group assignment, approached patients who screened positive (≥4 symptoms of panic or ≥ 1 symptoms of general anxiety (Spitzer *et al.* 1999)) plus all patients selected by their GP for a telephone interview (MINI-PLUS International Neuropsychiatric Interview). The MINI-PLUS is a semi-structured interview (van Vliet *et al.* 2000) used to classify psychiatric diagnoses according to the DSM-IV-TR (American Psychiatric Association 2001). GPs in both groups were notified of the diagnosis of patients they themselves had selected for the study but GPs in the control group were not notified about the diagnosis and participation of patients selected from the EMR. Patients were kept blinded for the group assignment of their GP until baseline. See Figure 1 for a flowchart of clusters and participants.

Intervention

Training of professionals in the intervention group

The mental health professionals were trained as care managers in a three day workshop about collaborative care (½ day), guided self-help (½ day), and CBT (2 days). The GPs attended a three hour workshop about the recognition of anxiety disorders, collaborative care and the prescription of medication following an algorithm. The six consultant psychiatrists participated in a one-hour meeting in which collaborative stepped care, the medication algorithm and the consultation process were discussed.

Collaborative stepped care intervention

For detailed information about the CSC intervention, see Box 1. CSC was provided by the care manager (who was preferably located in the primary care practice), GP and a consultant psychiatrist. The intervention consisted of three steps: CBT-based guided self-help (step one), cognitive behavioural therapy (CBT) (step two) and antidepressants according to a medication algorithm (step three). The care manager monitored response to treatment with the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988) and when a patient achieved remission (BAI ≤11), the care manager offered relapse prevention. If remission was not reached, the patient entered the next step. The GP and care manager were instructed to frequently discuss treatment progress with each other and to contact a psychiatrist (by e-mail, telephone or in person at the office of the psychiatrist) when they encountered difficulties during treatment or had any questions about treatment steps or medication. Furthermore, care managers were encouraged to attend three-weekly supervision sessions with a cognitive behavioural therapist. Adherence to the treatment protocol by care managers and GPs was further encouraged by regular telephone calls by a study psychologist (AM).

Care as usual (CAU)

The GPs and mental health professionals in the care as usual group received no additional training and they provided care as usual to their patients. In the Netherlands, GPs use national primary care treatment guidelines for anxiety disorders (Terluin *et al.* 2004). Care as usual could encompass prescription of antidepressants,

Box 1. Description of the intervention

Step 1: Guided self-help

Guided self-help consisted of a self-help manual based on cognitive behavioural principles, with psycho-education, cognitive behavioural exercises and a guided relaxation CD, which the patient worked through independently. The care manager coached the patient in this process in 5 short consultations (20 minutes) at the primary care practice spread over 12 weeks. In the first session, a treatment plan was discussed with the patient and signed by the patient, care manager and GP. The effectiveness of the guided self-help intervention was supported by a previous trial (van Boeijen *et al.* 2005).

Step 2: Cognitive behavioural therapy (CBT)

Two short duration CBT protocols (one for GAD and one for PD) and workbooks for patients were developed and adapted to the knowledge already gained in step one. Cognitive therapy as well as exposure were important elements in these protocols. CBT was delivered by the care manager in 6 sessions of 45 minutes. CBT has been proven effective in primary care in numerous studies (Cape *et al.* 2010).

Step 3: Antidepressants

The GP prescribed antidepressants and was encouraged to follow a medication algorithm which was based on (inter)national guidelines for anxiety disorders and an earlier study conducted in primary care (van der Feltz-Cornelis CM *et al.* 2006). The algorithm offered a choice of an SSRI, SNRI and a TCA, with instructions when to increase the dose or switch medication. We advised GPs to refrain from the use of anxiolytics (benzodiazepines) if possible.

Monitoring and relapse prevention

After each step, progress was evaluated with the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988). When the patient did not achieve remission (BAI score ≤ 11), the next step was offered. If necessary, the patient was referred to specialty mental health care. When remission was reached, the care manager provided relapse prevention through monthly follow-up calls with BAI administration until nine months after the end of treatment.

but also referral to the attached mental health professional, a primary care psychologist or to specialty mental health care. All patients in the control group were advised to seek treatment from their GP. We assessed the actual care provided in care as usual by a questionnaire.

Outcomes

Patients completed questionnaires at baseline and after 3, 6, 9 and 12 months, which were processed by research assistants who were blind to group assignment.

Primary outcome measure

The primary outcome measure was the reduction in anxiety symptoms, measured with the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988). This scale lists 21 symptoms of anxiety with a total score ranging from 0 to 63 points. The instrument has good psychometric properties (Ferguson 2000) and is suitable for assessing severity of the anxiety in primary care patients with anxiety disorders (Muntingh *et al.* 2011). The Overall Anxiety Severity and Impairment Scale (OASIS)(Norman *et al.* 2006) was used as a proxy for the severity of the anxiety at baseline.

Secondary outcome measures

Secondary outcome measure was time to first remission (BAI ≤ 11) or first response to treatment (≥50% reduction in score on the BAI) if remission was not achieved (Ader 2012). Depressive symptoms were measured with the Patient Health Questionnaire-9 (Spitzer *et al.* 1999) and quality of life was assessed with the Short-Form Health Survey-36 (Ware, Jr. & Sherbourne 1992) and the EuroQol EQ5D (Euroqol group 1995).

Adherence to treatment and content of care

Adherence to treatment and content of care were assessed using a checklist, which was administered to the GP (and to the care manager in the CSC group) by a research assistant 12 months after inclusion of the patient. The CSC checklist assessed whether the indicated steps in treatment and other essential elements such as monitoring with the BAI were applied. Missing data about remission of a patient were collected from patient questionnaires at follow-up. The CAU checklist assessed what kind of care the GP offered to patients (ie counselling or referral to primary or specialty mental health care). Medication use in both groups was measured by the patient-completed Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) (Hakkaart-van Roijen 2002).

Sample size calculation

The study was powered to detect a clinically relevant difference of 0.5 standard deviation (6 points) of CSC versus CAU on the continuous measure of the BAI, (Cohen 1988) with a power of 0.90 (α=0.05), and an estimated intraclass correlation coefficient (ICC) of 0.01 with 5 patients per cluster. With an expected loss to follow-up of 25% we aimed to include 89 patients per arm (Muntingh *et al.* 2009).

Data analysis

All analyses were done according to intention to treat principles. SPSS version 15.0 (SPSS Inc. 2006) was used for the analysis of baseline characteristics using t-tests for continuous measures and χ^2 tests for categorical variables. MLwiN V2 2.21 (Rasbash *et al.* 2011) was used for the linear multilevel regression analysis of the primary and secondary outcome measures. Multilevel analysis allows to model the variability of the outcome measure within clusters and allows to analyse a repeated measure design in the presence of missing data (Twisk 2006). In this cluster randomised trial, four levels were identified: (1) repeated measurements, (2) patients, (3) primary care practices and (4) care managers. An intraclass correlation coefficient (ICC) was calculated to give insight into the variability of the outcome measure at the level of the care manager (cluster). The effect size was calculated by dividing the between group difference by the pooled standard deviation (Cohens *d*). All p-values are two-tailed (α = 0.05).

Propensity scores were used to correct for possible bias introduced by cluster randomisation (van der Feltz-Cornelis CM *et al.* 2006; Muntingh *et al.* 2009). The OASIS score was used as a proxy for the severity of the anxiety at baseline (correlation between OASIS and BAI score at baseline: r = 0.69). Variables that differed significantly at baseline between CSC and CAU were tested for a significant interaction with treatment condition. No patients were excluded from the analysis, except for patients who already had a score of 11 or below on the BAI at baseline, who were excluded from the analysis on time to first remission or response.

Results

Patient characteristics

One hundred and eighty patients were included, 114 in the collaborative care group (83 selected by their GP and 31 selected in the EMR) and 66 in the care as usual group (16 patients selected by their GP and 50 selected in the EMR). Table 1 summarises the demographic and clinical characteristics of the participants. The mean age was 46.5 (SD 15.5) and the majority of the patients was female (68.3 %). Significant differences between groups were found in baseline BAI and OASIS score and antidepressant use. Patients in the intervention group scored higher on both anxiety scales than patients in the control group. Furthermore, significantly more patients in the control group used antidepressants at baseline compared to the intervention group.

Table 1. Baseline demographic and clinical patients characteristics for collaborative stepped care (CSC) and care as usual (CAU).

	CSC (N = 114)	**CAU (N = 66)**	**Total (N = 180)**	**p-value χ^2**
	N %	**N %**	**N %**	
Age, mean (SD)	44.98 (15.06)	49.08 (15.93)	46.48 (15.47)	.087
Anxiety score (BAI), mean (SD)[a]	24.59 (11.52)	20.04 (11.28)	22.09 (11.55)	.01*
Anxiety impairment score (OASIS), mean (SD)[a]	8.14 (4.14)	6.02 (4.26)	7.36 (1.30)	.001*
Depression score (PHQ9), mean (SD)[a]	9.40 (5.62)	8.98 (5.77)	9.25 (5.66)	0.64
Mental health component score (SF-36 MCS), mean (SD)[a]	32.56 (11.26)	35.74 (13.00)	33.72 (11.99)	0.09
Physical health component score (SF-36 PCS), mean (SD)[a]	48.43 (8.73)	47.75 (10.38)	48.18 (9.35)	0.64
Euroqol EQ-5D score, mean (SD)[a]	0.67 (0.17)	0.70 (0.14)	0.68 (0.16)	0.26
Gender				.09
Male	31 27.2	26 39.4	57 31.7	
Female	83 72.8	40 60.6	123 68.3	

Country of birth							.50
The Netherlands	101	89.4	58	89.2	159	89.3	
Other European country	4	3.5	1	1.5	5	2.8	
Non-European country	8	7.1	6	9.2	14	7.9	
Level of education							.709
Low	51	44.7	29	44.6	80	44.7	
Intermediate	42	36.8	21	32.3	63	35.2	
High	21	18.4	15	23.1	36	20.1	
Married / living together	65	57.5	41	63.1	106	59.6	.231
Primary diagnosis							.943
PD	48	42.1	29	43.9	77	42.8	
GAD	32	28.1	17	25.8	49	27.2	
PD & GAD	34	29.8	20	30.3	54	30.0	
Age of onset, mean (SD)							
PD	79	30.35 (13.76)	46	31.11 (13.47)	125	30.63 (13.60)	0.77
GAD	60	30.62 (15.08)	32	34.13 (18.16)	92	31.84 (16.20)	0.33
Co-morbid depression	34	29.8	22	33.3	56	31.1	0.624
Psychological treatment in the past	62	56.9	43	70.5	105	61.8	.080
Use of antidepressants	23	21.9	23	38.3	46	27.9	.024*
Nr of psychiatric diagnoses, mean (SD)	2.59 (1.54)		2.26 (1.17)		2.47 (1.42)		.107
Nr of chronic conditions, mean (SD)	1.35 (1.57)		1.58 (1.49)		1.4 (1.54)		.348

[a] Uncorrected baseline score

*p<0.05

Retention

Three clusters (two in CAU and one in CSC) were excluded because they did not include any patients. The follow-up questionnaires were returned by 152 patients (85%) at three months, 137 patients (76%) at six months, 134 patients (74%) at nine months and 135 patients (75%) at twelve months. Seventeen patients did not return any of the follow-up questionnaires. There were no significant differences in dropout rates between the two conditions.

Results primary outcome measure

Clusters ranged from 1 to 15 included patients (median 5) and the ICC was 0.038. A significantly larger reduction was found in mean BAI score from baseline to three, six, nine and twelve months in CSC compared to CAU (see Table 2 and Figure 2). The effect sizes of the difference between mean BAI scores at the follow-up measurements were small to moderate. The results were not significantly influenced by antidepressant use at baseline.

Results secondary outcome measures

No significant differences between CSC and CAU were found for time to first remission (difference in change score (b) = 0.33, 95% CI -0.16 to 0.81), time to first response (b=-0.43, 95% CI -1.32 to 0.45) or the absence of response or remission (b=-0.003, 95% CI -0.33 to 0.33). Significant differences were found at three and twelve months on depressive symptoms (PHQ-9) and mental health (SF-36), and at twelve months on health related quality of life (EQ5D), all in favour of CSC (see Appendix A).

Table 2: Mean BAI scores, effect size and change scores of CSC (N=114) versus CAU (N=66) from baseline to 3, 6, 9 and 12 months

	CSC (N=114)		**CAU (N=66)**		**CSC vs. CAU**				
BAI score[a]	**Mean**	95% CI	**Mean**	95% CI	ES [b]	95% CI	**Δ diff.** [c]	95% CI	**P** [d]
Baseline	**23.67**	20.61-26.72	**21.40**	18.74-24.06					
3 months	**15.14**	12.13-18.14	**17.98**	15.02-20.94	**0.23**	0.001 -0.45	**-5.11**	-8.28--1.94	0.001
6 months	**12.80**	9.80-15.81	**15.19**	12.56-17.82	**0.20**	-0.04-0.44	**-4.65**	-7.93--1.38	0.01
9 months	**11.96**	8.94-14.98	**15.36**	12.72-18.00	**0.28**	0.04-0.52	**-5.67**	-8.97--2.36	0.001
12 months	**12.21**	9.20-15.22	**16.79**	14.16-19.42	**0.38**	0.14-0.62	**-6.84**	-10.13--3.55	0.001

a The multilevel model was corrected for propensity score and anxiety severity at baseline (OASIS score)

b Between-group effect size was calculated by the difference in means, divided by the pooled standard deviation

c Difference in reduction in BAI score from baseline to 3, 6, 9 and 12 months (CSC vs. CAU)

d P-value of the difference in change scores, calculated with the Wald-test

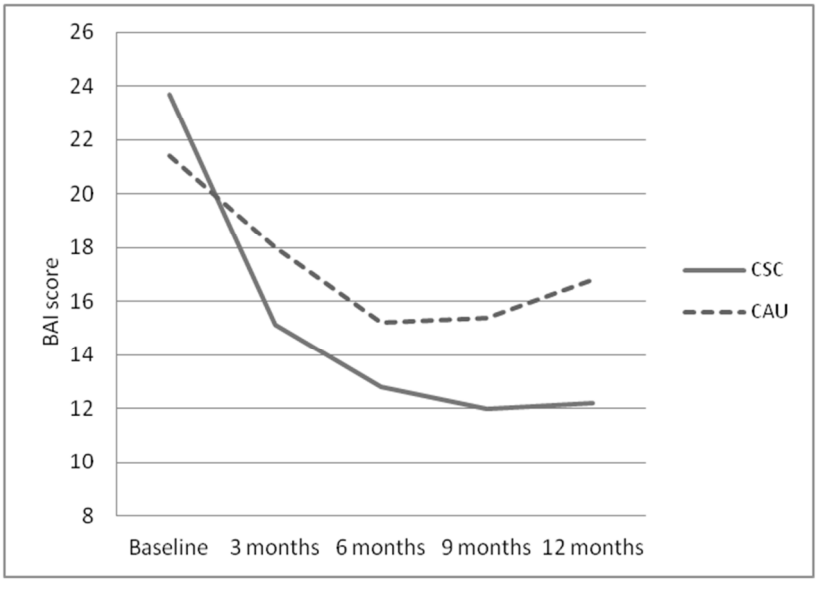

Figure 2. Mean score on the Beck Anxiety Inventory (BAI) over time for CSC and CAU, corrected for propensity score and OASIS score at baseline.

Adherence to treatment and content of care

Checklists about adherence to treatment and content of care were retrieved of 103 CSC patients (90.4%) and 56 CAU patients (84.8%). Table 3 shows that half of the CSC patients achieved remission after step 1. However, many patients (N=42, 41%) discontinued the CSC program before achieving remission of whom 11 (26%) were referred to another mental health professional. The psychiatrists were consulted for only 10 (22%) of the patients who discontinued the program.

Table 3 Proportion of patients in which essential elements of collaborative stepped care were indicated and applied (N=103)

Elements of CSC	Indicated patient group (N=103)	Element indicated	Element applied	Partly applied	Not applied	Partly/not applied
		N (%)[1]	N (%)[2]	N	N	%[2]
Step 1	All patients	103 (100%)	80 (78%)	15	8	(22%)
Step 2	Patients who concluded step 1, but did not achieve remission after step 1	28 (27%)	9 (32%)	1	18	(68%)
Step 3	Patients who concluded step 2, but did not achieve remission after step 2	5 (5%)	2 (40%)	0	3	(60%)
Relapse prevention	Patients who successfully concluded step 1, 2 or 3	58 (56%)	34 (59%)	0	24	(41%)
Sessions monitored with BAI	Patients who started step 1	95 (92%)	71 (75%)	21	3	(25%)
Consultation with psychiatrist	Patients who did not follow indicated steps	45 (44%)	10 (22%)	0	35	(78%)

[1] % of CSC patients with sufficient data (N=103)

[2] N° of patients with element (partly/not) applied/N° of patients with indication for element

We formed subgroups of patients in both CSC and CAU based on the form of treatment they received. Table 4 shows the outcome at twelve months for the different subgroups, with CAU patients who received no treatment as the reference group. Only CSC patients who at least concluded step 1 had a significantly lower score than the CAU "no treatment" group. Non-adherent CSC patients differed from other CSC patients on various baseline variables: they were more often widowed or divorced (34.7 vs. 7.6%), were selected from the EMR instead of selected by their GP (56.5% vs. 18.8%), had a low level of education (65.2% vs. 37.5%), were taking antidepressants at baseline (42.1% vs. 14.3%), were older (mean 53.6 vs. 42.8) and suffered from more chronic conditions (mean 2.1 vs. 1.3).

Table 4 Content of care in the CSC group (N=103) and in the CAU group (N=63), related to the reduction in BAI score after 12 months[a]

CSC (N=103)	**N , %**	**Reduction in BAI score at 12 months Mean [95% CI]**
Guided self-help*	51 (49.5%)	-7.14 [-13.58- -0.69]
Guided self-help+	29 (28.2%)	-7.32 [-14.19- -0.45]
CBT	*7 (6.8%)*	
Antidepressants	*19 (18.4%)*	
CBT and antidepressants	*3 (2.9%)*	
Non-adherent (guided self-help ≤2 sessions)	23 (22.3%)	-1.17 [-9.11-6.78]
CAU (N=63)	**N , %**	
Counselling**	14 (22.2%)	-3.55 [-11.35-4.25]
Antidepressants	23 (36.5%)	3.37 [-3.72-10.47]
with counselling	*11 (17.5%)*	
Specialty mental health care	11 (17.5%)	0.08 [-8.68-8.85]
No treatment/non-adherent	15 (23.8%)	*Reference group*

[a] Analysis with a multilevel linear regression model, correcting for propensity score and baseline severity (OASIS)

*≥3 sessions (no medication or medication unknown)

**By GP, psychiatric nurse or primary care psychologist

Discussion

The results of this study indicate that collaborative stepped care is more effective in reducing anxiety symptoms than care as usual, both in the short and the long term. The largest difference between the two groups was found after twelve months, suggesting a relapse of the anxiety in care as usual patients and a persistence of a positive effect in the collaborative stepped care patients. This may be due to the activating elements in the collaborative stepped care treatment and the relapse prevention program provided to a significant proportion of collaborative stepped care patients.

The anxiety disorders in our sample were fairly chronic, with a mean age of onset of 31, while the mean age of participants was 46. This supports the idea that anxiety disorders in primary care need a continuous and multidisciplinary approach as offered in collaborative stepped care.

The effectiveness of CSC in this study is generally comparable with the outcomes of collaborative care studies without stepped care, although the effect sizes in the early stages of the trial (3 to 9 months) tended to be smaller in our study, which may have to do with our stepped care approach. Moreover, in previous collaborative care studies, significant differences in response and remission rates were found (Roy-Byrne *et al.* 2001; Rollman *et al.* 2005; Roy-Byrne *et al.* 2005b; Roy-Byrne *et al.* 2010). We did not find such a difference, which may be explained by a large proportion of patients in the care as usual group who did either not improve or showed a worsening of symptoms. This effect is visible on a continuous outcome measure, but minimally on a dichotomous outcome measure.

Strengths and limitations

A strength of this study is the naturalistic setting in which care was provided. The participating care managers, GPs and psychiatrists were all professionals working in the field in contrast to care managers and psychiatrists in previous collaborative care studies (Curran *et al.* 2012). Therefore, the results are likely to approximate the results of collaborative stepped care in everyday practice. Indeed, the CAU patients in our study showed a similar improvement over one year as seen in an observational cohort

in Dutch primary care (van Beljouw *et al.* 2010). Another strength of this study is that we used multilevel analysis, correcting for differences on the level of the health care professionals and accurately estimating the effects on the level of the participants. Furthermore, we did collect data about the actual content of care in both groups, while this information is often missing in collaborative care trials (Gilbody *et al.* 2006). The choice of a cluster randomised trial was based on the notion that there is a risk of substantial contamination in patient randomised trials using complex interventions such as collaborative care (Richards *et al.* 2008). However, cluster randomisation carries a risk of selection bias. To diminish this risk, all patients were interviewed with the MINI PLUS by a blinded interviewer and patients were kept blinded for the condition of their GP until baseline. Despite of these efforts, differences between the CSC group and the CAU group at baseline appeared. Patients in the collaborative stepped care group had a higher severity of anxiety and did less often take antidepressants at baseline. In the analysis we corrected for possible errors introduced by selection bias with propensity scores and we corrected for the anxiety severity at baseline. Antidepressant use at baseline did not have a significant influence on treatment effect. Another limitation of this trial is that, despite extensive supervision and instruction of the care managers and GPs, the stepped care model was not optimally implemented. A significant proportion of patients did either not complete step 1 (22%) or did not continue to step 2 while remission was not yet achieved (18%). Some of these patients (N=11, 26%) were referred to another professional, while other patients may have perceived no further need for treatment because of a decline in symptoms or the presence of medical or social problems that required attention. The relatively low rate of patients continuing to the second step compares to the results of a recent stepped care trial (Seekles *et al.* 2011) and an analysis of the implementation of stepped care in routine practice (Richards *et al.* 2012; Taylor *et al.* 2012). However, it does warrant attention because patients who have residual symptoms of anxiety are prone to a relapse of the anxiety disorder (Karsten *et al.* 2011).

Further research and analysis

To further improve the effectiveness of CSC, efforts may be needed to increase patient adherence, for example by offering patients a choice out of different

interventions at the start of treatment (Kwan *et al.* 2010) (matched care) and evaluating the treatment plan with the patient in an early stage of treatment. Provider adherence may be enhanced by increasing the case load and supervision of care managers, intensifying the role of psychiatrists, placing more emphasis on relapse prevention and using a web-based tracking system to guide professionals in providing care and communication (Roy-Byrne *et al.* 2010; Huijbregts *et al.* 2012). Another approach, exploring possibilities for matched care, might be to develop a prediction model resulting in a risk profile for early treatment drop-out or non-response. Following our exploratory analysis of variables related to non-adherence, living situation, level of education, antidepressant use, age, co-morbid chronic diseases and the clinical evaluation of the GP may be good candidates for such a prediction model. The cost-utility of CSC will be described in a future paper.

Conclusions

This is the first study, to our knowledge, to demonstrate the effectiveness of collaborative stepped care for anxiety disorders, with guided self-help as a first step, compared to care as usual. Despite of a suboptimal implementation of the stepped care model, CSC patients experienced a greater decrease in anxiety symptoms, which was maintained over time. Effective elements in CSC may be the collaboration between professionals, the guided self-help method and relapse prevention. Policy efforts are needed to facilitate implementation of CSC in primary care.

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REFERENCES

Ader, H. A composite score that combines response and remission. Available from: www.jvank.nl/Trimbos/Remres/Composite.pdf. 2012.

American Psychiatric Association (2001). *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).* American Psychiatric Publishing: Washington, DC.

Andlin-Sobocki, P. & Wittchen, H. U. (2005). Cost of anxiety disorders in Europe. *Eur J Neurol.* **12 Suppl 1**, 39-44.

Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* **56 (6)**, 893-897.

Bijl, R. V. & Ravelli, A. (2000). Psychiatric morbidity, service use, and need for care in the general population: results of The Netherlands Mental Health Survey and Incidence Study. *Am.J.Public Health* **90**, 602-607.

Bower, P. & Gilbody, S. (2005). Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry* **186**, 11-17.

Cape, J., Whittington, C., Buszewicz, M., Wallace, P. & Underwood, L. (2010). Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. *BMC Med* **8**, 38.

Cohen, J. (1988). *Statistical power analysis for the behavioral science. Second Edition.* Lawrence Erlbaum Associates,Inc.: Hillsdale.

Coull, G. & Morris, P. G. (2011). The clinical effectiveness of CBT-based guided self-help interventions for anxiety and depressive disorders: a systematic review. *Psychol Med* **41**, 2239-2252.

Curran, G. M., Sullivan, G., Mendel, P., Craske, M. G., Sherbourne, C. D., Stein, M. B., McDaniel, A. & Roy-Byrne, P. (2012). Implementation of the CALM intervention for anxiety disorders: a qualitative study. *Implement.Sci* **7**, 14.

Euroqol group (1995). *Eq-5D user guide.* Sanders instituut, EUR: Rotterdam.

Ferguson, R. J. Using the Beck Anxiety Inventory in Primary Care. Maruish, M. E. Handbook of psychological assessments in primary care settings. 509-535. 2000. Mahwah, NJ, Lawrence Erlbaum.

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern.Med* **166**, 2314-2321.

Greenberg, P. E., Sisitsky, T., Kessler, R. C., Finkelstein, S. N., Berndt, E. R., Davidson, J. R., Ballenger, J. C. & Fyer, A. J. (1999). The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry* **60**, 427-435.

Hakkaart-van Roijen, L. (2002). Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in Dutch). Institute for Medical Technology Assessment: Rotterdam.

Huijbregts, K. M., de Jong, F. J., Van Marwijk, H. W. J., Beekman, A. T. F., Adèr, H., Hakkaart-Van Roijen, L., Unutzer, J. & Van der Feltz-Cornelis C.M. (2012). A target-driven Collaborative Care model for Major Depressive Disorder is effective in primary care in the Netherlands. A Randomized Clinical Trial from the Depression Initiative. *Journal of Affective Disorders,* accepted for publication.

Karsten, J., Hartman, C. A., Smit, J. H., Zitman, F. G., Beekman, A. T. F., Cuijpers, P., Does, A. J. W., Ormel, J., Nolen, W. A. & Penninx, B. W. J. H. (2011). Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *British Journal of Psychiatry* **198**, 206-212.

Kendall, T., Cape, J., Chan, M. & Taylor, C. (2011). Management of generalised anxiety disorder in adults: summary of NICE guidance. *Bmj* **342**, c7460.

Kroenke, K., Spitzer, R. L., Williams, J. B., Linzer, M., Hahn, S. R., deGruy, F. V. & Brody, D. (1994). Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Archives of Family Medicine* **3**, 774-779.

Kwan, B. M., Dimidjian, S. & Rizvi, S. L. (2010). Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behav Res Ther* **48**, 799-804.

Muntingh, A. D., van der Feltz-Cornelis CM, van Marwijk, H. W., Spinhoven, P., Penninx, B. W. & van Balkom, A. J. (2011). Is the Beck Anxiety Inventory a good tool to assess the severity of anxiety? A primary care study in The Netherlands Study of Depression and Anxiety (NESDA). *BMC.Fam.Pract.* **12**, 66.

Muntingh, A. D. T., van der Feltz-Cornelis CM, Van Marwijk, H. W. J., Spinhoven, P., Assendelft, W. J. J., de Waal, M. W., Hakkaart-van, R. L., Ader, H. J. & Van Balkom, A. J. L. M. (2009). Collaborative stepped care for anxiety disorders in primary care: aims and design of a randomized controlled trial. *BMC Health Services Research* **9**, 159.

National Institute for Health and Clinical Excellence (2011). Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. NICE clinical guideline 113.

Norman, S. B., Cissell, S. H., Means-Christensen, A. J. & Stein, M. B. (2006). Development and validation of an Overall Anxiety Severity And Impairment Scale (OASIS). *Depress.Anxiety* **23**, 245-249.

Olatunji, B. O., Cisler, J. M. & Tolin, D. F. (2007). Quality of life in the anxiety disorders: a meta-analytic review. *Clin Psychol Rev* **27**, 572-581.

Rasbash, J., Charlton, C., Browne, B. J., Healy, M., & Cameron, B. MLWiN Version 2.1. (2011). University of Bristol, Centre for Multilevel Modelling.

Richards, D. A. & Borglin, G. (2011). Implementation of psychological therapies for anxiety and depression in routine practice: two year prospective cohort study. *J Affect Disord* **133**, 51-60.

Richards, D. A., Bower, P., Pagel, C., Weaver, A., Utley, M., Cape, J., Pilling, S., Lovell, K., Gilbody, S., Leibowitz, J., Owens, L., Paxton, R., Hennessy, S., Simpson, A., Gallivan, S., Tomson, D. & Vasilakis, C. (2012). Delivering stepped care: an analysis of implementation in routine practice. *Implement.Sci* **7**, 3.

Richards, D. A., Lovell, K., Gilbody, S., Gask, L., Torgerson, D., Barkham, M., Bland, M., Bower, P., Lankshear, A. J., Simpson, A., Fletcher, J., Escott, D., Hennessy, S. & Richardson, R. (2008). Collaborative care for depression in UK primary care: a randomized controlled trial. *Psychological Medicine* **38**, 279-287.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.

Roy-Byrne, P. P., Wagner, A. W. & Schraufnagel, T. J. (2005a). Understanding and treating panic disorder in the primary care setting. *Journal of Clinical Psychiatry* **66 Suppl 4**, 16-22.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005b). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.

Roy-Byrne, P. P., Davidson, K. W., Kessler, R. C., Asmundson, G. J., Goodwin, R. D., Kubzansky, L., Lydiard, R. B., Massie, M. J., Katon, W., Laden, S. K. & Stein, M. B. (2008). Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* **30**, 208-225.

Roy-Byrne, P. P. & Wagner, A. (2004). Primary care perspectives on generalized anxiety disorder. *J Clin Psychiatry* **65 Suppl 13**, 20-26.

Roy-Byrne, P. P., Katon, W., Cowley, D. S. & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* **58**, 869-876.

Seekles, W., van Straten, A., Beekman, A., van Marwijk, H. & Cuijpers, P. (2011). Stepped care treatment for depression and anxiety in primary care. a randomized controlled trial. *Trials* **12**, 171.

Spijker, J., van Vliet, I. M., Meeuwissen, J. A. C. & Van Balkom, A. J. L. M. (2010). [Update of the multidisciplinary guidelines for anxiety and depression]. *Tijdschr Psychiatr* **52**, 715-718.

Spitzer, R. L., Kroenke, K. & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama* **282**, 1737-1744.

SPSS Inc. SPSS 15.0 for Windows. 2006. Chicago.

Stein, M. B., Roy-Byrne, P. P., Craske, M. G., Campbell-Sills, L., Lang, A. J., Golinelli, D., Rose, R. D., Bystritsky, A., Sullivan, G. & Sherbourne, C. D. (2011). Quality of and patient satisfaction with primary health care for anxiety disorders. *J Clin Psychiatry* **72**, 970-976.

Stein, M. B., Sherbourne, C. D., Craske, M. G., Means-Christensen, A., Bystritsky, A., Katon, W., Sullivan, G. & Roy-Byrne, P. P. (2004). Quality of care for primary care patients with anxiety disorders. *Am J Psychiatry* **161**, 2230-2237.

Taylor, S., Abramowitz, J. & Mckay, D. (2012). Non-adherence and non-response in the treatment of anxiety disorders. *J Anxiety Disord*.

Terluin, B., Grol, M. H., Pijnenborg, L., & Goudswaard, A. N. 2005, [Summary of the practice guideline 'Anxiety disorders' (first revision) from the Dutch College of General Practitioners].

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease, D. E., Jr. & Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med* **42**, 525-538.

Twisk, J. W. R. (2006). *Applied Multilevel Analysis*. Cambridge University Press: Cambridge.

van Beljouw, I. M., Verhaak, P. F., Cuijpers, P., van Marwijk, H. W. & Penninx, B. W. (2010). The course of untreated anxiety and depression, and determinants of poor one-year outcome: a one-year cohort study. *BMC Psychiatry* **10**, 86.

van Boeijen, C. A., van Oppen, P., van Balkom, A. J., Visser, S., Kempe, P. T., Blankenstein, N. & van Dyck, R. (2005). Treatment of anxiety disorders in primary care practice: a randomised controlled trial. *Br J Gen Pract.* **55**, 763-769.

van der Feltz-Cornelis CM, van, O. P., Ader, H. J. & van, D. R. (2006). Randomised controlled trial of a collaborative care model with psychiatric consultation for persistent medically unexplained symptoms in general practice. *Psychother Psychosom* **75**, 282-289.

van Vliet, I. M., Leroy, H., & van Megen, H. J. M. (2000). De MINI-Internationaal neuropsychiatrisch interview: een kort gestructureerd diagnostisch interview voor DSM-IV en ICD-10 psychiatrische stoornissen. [The Mini-international Neuropsychiatric Interview: A short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. In Dutch].LUMC: Leiden.

Ware, J. E., Jr. & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med.Care* **30**, 473-483.

Yonkers, K. A., Bruce, S. E., Dyck, I. R. & Keller, M. B. (2003). Chronicity, relapse, and illness--course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress.Anxiety* **17**, 173-179.

Appendix A

Mean scores, effect sizes and change scores from baseline derived form the multilevel models[a] for collaborative stepped care (CSC) versus care as usual (CAU)

SF-36 mental health component score	**M CSC**	95% CI-	95% CI+	**M CAU**	95% CI-	95% CI-	ES	95% CI-	95% CI+	**Δ diff.**	95% CI-	95% CI+	P
Baseline	**33.37**	29.84	36.90	**36.12**	32.99	39.25							
Three months	**40.01**	36.60	43.43	**38.72**	35.71	41.74	**0.09**	-0.14	0.32	**4.05**	0.41	7.68	0.03*
Six months	**41.60**	38.09	45.11	**40.85**	37.74	43.96	**0.06**	-0.19	0.30	**3.51**	-0.33	7.34	0.07
Nine months	**42.53**	39.00	46.06	**44.27**	41.14	47.40	**0.13**	-0.12	0.38	**1.01**	-2.87	4.90	0.61
Twelve months	**43.64**	40.17	47.11	**39.99**	36.93	43.06	**0.27**	0.02	0.51	**6.40**	2.62	10.18	0.001*
SF-36 physical health component score	**M CSC**	95% CI-	95% CI+	**M CAU**	95% CI-	95% CI-	ES	95% CI-	95% CI+	**Δ diff.**	95% CI-	95% CI+	P
Baseline	**47.95**	44.95	50.95	**47.81**	45.22	50.41							
Three months	**50.16**	47.61	52.71	**47.99**	45.77	50.21	**0.21**	-0.02	0.44	**2.03**	-0.17	4.24	0.07
Six months	**49.68**	47.09	52.27	**48.93**	46.67	51.19	**0.07**	-0.17	0.32	**0.61**	-1.71	2.94	0.60
Nine months	**50.01**	47.40	52.62	**48.15**	45.87	50.43	**0.19**	-0.06	0.44	**1.72**	-0.64	4.08	0.15
Twelve months	**49.70**	47.12	52.27	**49.25**	47.01	51.48	**0.04**	-0.20	0.29	**0.31**	-1.97	2.59	0.79

EQ5D		M CSC	95% CI-	95% CI+	M CAU	95% CI-	95% CI-	ES	95% CI-	95% CI+	Δ diff.	95% CI-	95% CI+	P
	Baseline	**0.68**	0.62	0.74	**0.70**	0.70	0.70							
	Three months	**0.76**	0.70	0.82	**0.72**	0.72	0.72	**0.05**	-0.18	0.27	**0.04**	-0.02	0.09	0.21
	Six months	**0.73**	0.67	0.78	**0.70**	0.70	0.70	**0.12**	-0.12	0.36	**0.05**	-0.01	0.11	0.09
	Nine months	**0.75**	0.70	0.81	**0.75**	0.75	0.75	**0.09**	-0.15	0.33	**0.00**	-0.06	0.06	0.90
	Twelve months	**0.79**	0.74	0.85	**0.72**	0.72	0.72	**0.21**	-0.03	0.45	**0.07**	0.01	0.13	0.02*

PHQ9 score		M CSC	95% CI-	95% CI+	M CAU	95% CI-	95% CI-	ES[b]	95% CI-	95% CI+	Δ diff.[c]	95% CI-	95% CI+	P[d]
	Baseline	**9.36**	7.49	11.22	**8.72**	0.82	7.12							
	Three months	**6.12**	4.49	7.74	**8.04**	0.72	6.64	**0.19**	-0.04	0.41	**-1.93**	-3.41	-0.44	0.01*
	Six months	**5.96**	4.30	7.61	**6.27**	0.73	4.83	**0.05**	-0.19	0.29	**-0.95**	-2.51	0.61	0.23
	Nine months	**5.02**	3.35	6.69	**5.94**	0.74	4.49	**0.04**	-0.20	0.28	**-0.91**	-2.51	0.68	0.26
	Twelve months	**4.87**	3.22	6.51	**6.60**	0.73	5.17	**0.17**	-0.07	0.41	**-1.73**	-3.27	-0.19	0.03*

a The multilevel models were corrected for propensity score
b Between-group effect size calculated by the difference in means score at a time-point, divided by the pooled standard deviation.
c Difference in change score from baseline to 3, 6, 9 and 12 months (CSC vs. CAU)
d P-value of the difference in change scores, calculated with the Wald-test
* $p < 0.05$

Chapter 4

Cost-utility analysis of a Collaborative Stepped Care intervention for panic - and generalised anxiety disorder in primary care

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Abstract

Background: Generalised anxiety and panic disorder are a burden on society because they have a significant adverse effect on the quality of life and are costly. Collaborative Stepped Care has proven to be an effective treatment. The aim of this study was to evaluate the cost-utility of a Collaborative Stepped Care intervention for panic disorder and generalised anxiety disorder in primary care compared to Care As Usual from a societal perspective.

Methods: The design of the study was a two armed cluster randomised controlled trial. In total 43 primary care practices in the Netherlands participated in the study. Patients were selected by their general practitioner or by a research assistant using a screening instrument. To classify DSM-IV disorders, these patients were approached for a diagnostic interview (MINI-PLUS). Eventually, 180 patients, diagnosed with panic disorder or generalised anxiety disorder were included in the study (114 Collaborative Stepped Care, 66 Care As Usual). Baseline measures and follow up measures (3, 6, 9 and 12 months) were assessed using questionnaires. We applied the TiC-P, the SF-HQL and the EQ-5D respectively measuring health care utilisation, production losses and general health related quality of life.

Results: The average annual direct medical costs in the Collaborative Stepped Care group were 1,854 Euro (95% CI 1,726 to 1,986) compared to 1,503 Euro (95 % CI 1,374 to 1,664) in the Care As Usual group. The average quality of life years (QALY's) gained was higher in the Collaborative Stepped Care group, with a difference of 0.05 (95% CI 0.04 to 0.07). The direct medical costs were also higher in the Collaborative Stepped Care group, leading to an incremental cost-effectiveness ratio (ICER) of 6,385 Euro per QALY. At a threshold of 20,000 Euro/QALY the probability that the ratio is acceptable was more than 90%. Inclusion of the productivity costs, consequently reflecting the full societal costs, decreased the ratio even more.

Conclusion: The study showed that Collaborative Stepped Care was a cost effective intervention for panic disorder and generalised anxiety disorder and was even dominant when a societal perspective was taken.

Trial registration: Netherlands Trial Register NTR1071

Introduction

Generalised anxiety disorder (GAD) and panic disorder (PD) occur in 4% to 8% of patients in primary care (Kroenke *et al.* 2007; Lieb *et al.* 2004; Roy-Byrne *et al.* 2004; Roy-Byrne *et al.* 2005a). They are associated with an adverse effect on quality of life (Barrera & Norton, 2009; Beard *et al.* 2010; Bereza *et al.* 2009; Olatunji *et al.* 2007), higher health care use, reduced productivity and higher health care costs compared to non-anxious individuals (Andlin-Sobocki & Wittchen, 2002; Bereza *et al.* 2009).

Although they are a great burden to society, anxiety disorders are not sufficiently recognised and treated by general practitioners (GPs) (Fernandez *et al.* 2007; Roy-Byrne *et al.* 2002; Stein *et al.* 2004; Stein *et al.* 2011). Whereas pharmacological treatment is frequently initiated for generalised anxiety and panic disorder (Smolders *et al.* 2008; Stein *et al.* 2004), research indicates that compared to care as usual, cognitive behavioural therapy is more cost-effective (Heuzenroeder *et al.* 2004), preferred by most patients (Prins *et al.* 2009; van Schaik *et al.* 2004; Walters *et al.* 2008) and leads to more sustainable effects (Heuzenroeder *et al.* 2004; Nadiga *et al.* 2003). Another problem in current primary care is that the continuity of care is not ensured, because response to treatment is rarely monitored. Consequently, there is no opportunity to adapt treatment accordingly (Bakker *et al.* 2010; Katon *et al.* 2001) or intervene post-treatment when considered necessary (Roy-Byrne *et al.* 2004; Roy-Byrne *et al.* 2005a). Continuity of care is important because anxiety disorders often run a chronic or intermittent course (Roy-Byrne *et al.* 2004; Roy-Byrne *et al.* 2005a).

To address these problems, collaborative care models have been developed. These days a promising treatment model is Collaborative Stepped Care (Bower & Gilbody, 2005). In Collaborative Stepped Care pharmacological treatment is only indicated if cognitive behavioural therapy is insufficient. In addition, Collaborative Stepped Care may work in a more efficient way in terms of resource use and costs, because of the focus on low intensity treatment in the first steps (Bower & Gilbody, 2005).

There is evidence that the collaborative care model is an effective intervention for patients with anxiety disorders (Rollman *et al.* 2005; Roy-Byrne *et al.* 2010; Roy-Byrne *et al.* 2005b; Roy-Byrne *et al.* 2001). Recently, a study on the effectiveness of Collaborative Stepped Care showed that it is more effective in reducing anxiety

symptoms in panic and generalised anxiety disorder than care as usual (Muntingh *et al.* 2012). Until now there have been no studies on the cost-effectiveness of the Collaborative Stepped Care model for anxiety disorders. Some research has been done regarding the cost-effectiveness of collaborative care for major depression which suggests that collaborative care is a cost-effective intervention (van Steenbergen-Weijenburg *et al.* 2010) and is associated with good economic value (Jacob *et al.* 2012). A study of Joesch and colleagues (2011) showed that a collaborative care intervention for patients with panic disorder, generalised anxiety disorders, social anxiety disorders and posttraumatic stress disorder, provided higher benefits and only slightly increased costs, compared to usual care (Joesch *et al.* 2011). Two previous studies concerning panic disorders indicate that collaborative care may be cost-effective (Katon *et al.* 2006) or even dominant (Katon *et al.* 2002) compared to usual care. However, these studies were conducted in the United States, so results may not be easily generalised to the European health care setting. Furthermore, none of the studies used a stepped component in collaborative care. Finally, most of these studies did not take a societal perspective.

Hence, the aim of this study was to evaluate the cost-utility of a Collaborative Stepped Care intervention compared to a care as usual intervention in patients with panic disorder and generalised anxiety disorder in the primary care setting from a societal perspective.

Methods

Recruitment and randomisation

This cost-utility analysis was part of a two armed cluster randomised trial to evaluate the effectiveness of the Collaborative Stepped Care program. Study methods are described in detail elsewhere and are summarised in this section (Muntingh *et al.* 2009). The study was conducted at 43 primary care practices (PCPs) with 63 GPs in the region of a large mental health centre (Rivierduinen) in the Netherlands. The PCPs assigned 31 mental health professionals, consisting of 3 psychologists and 28 psychiatric nurses. Six experienced psychiatrists working in the mental health care centre operated as consultant psychiatrists for the intervention group. Cluster randomisation was executed at the level of the mental health professionals who were randomised to Collaborative Stepped Care or Care As Usual. A first selection of patients was performed by the GPs or by a research assistant using the electronic medical records (EMR) of patients. The selected patients were then assessed by a self-report screening scale, the Patient Health Questionnaire anxiety subscales (PHQ) (Spitzer *et al.* 1999). The patients who were selected from the EMR and who were considered to be screen positive and all patients selected by the GP were approached for a telephone interview to detect mental disorders (MINI PLUS International Neuropsychiatric interview) (van Vliet *et al.* 2007).

Intervention

The intervention consisted of four integrated evidence-based treatment steps (Figure 1): Guided self-help (van Boeijen *et al.* 2005), cognitive behavioural therapy, antidepressants according to a medication algorithm and optimisation of medication in primary care or referral to secondary care. After each step remission was determined with the Beck Anxiety Inventory (BAI)(Beck *et al.* 1988). If a patient did not achieve the criteria for remission (BAI≤11) after a certain step in the program the patient moved to the next step, otherwise the patient started a relapse prevention program. Mental health professionals (care managers) and general practitioners randomised to the Collaborative Stepped Care group were trained in the intervention. Patient adherence was encouraged by psycho-education, goal setting and by frequent

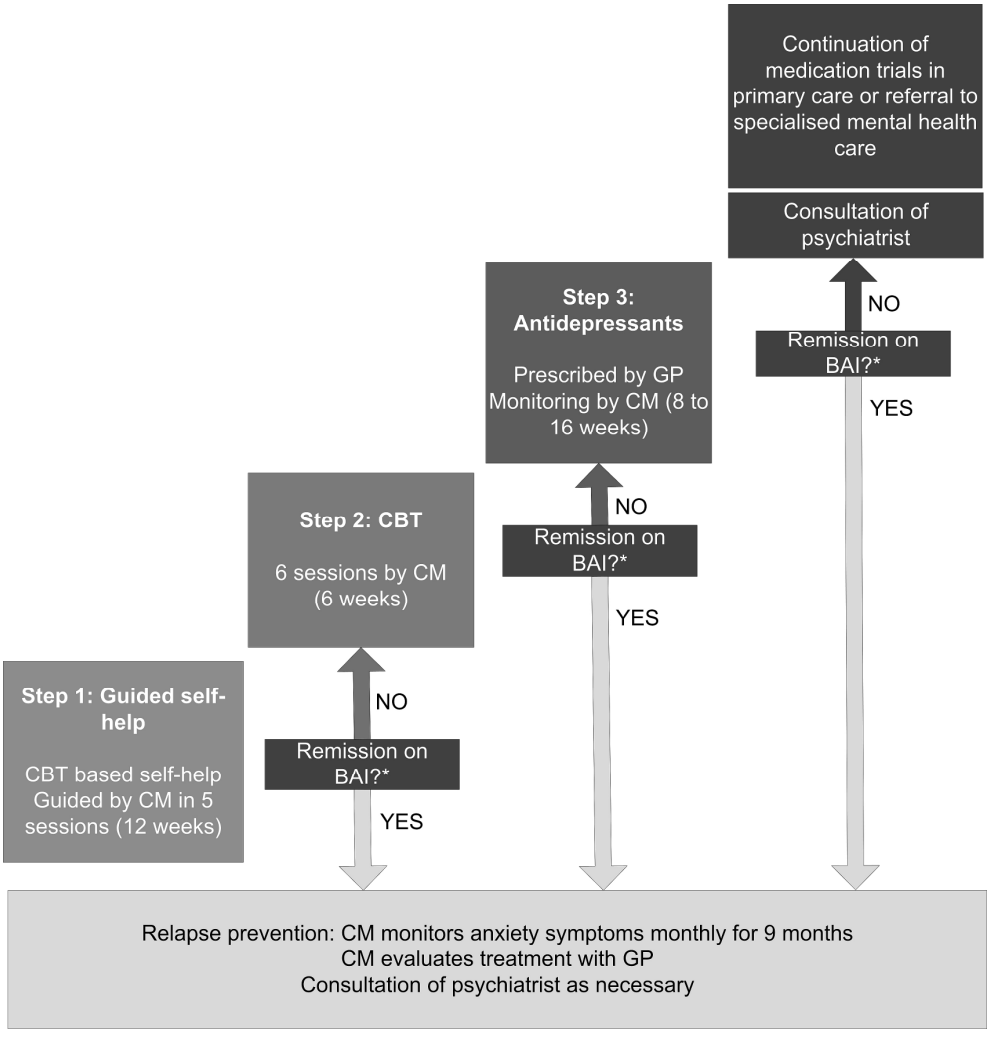

Figure 1: Collaborative Stepped Care treatment algorithm.

**Remission = BAI ≤ 11; BAI = Beck Anxiety Inventory; CM = care manager; GP = general practitioner.*

follow-up appointments in which both adherence and progress were evaluated. If a patient achieved remission after step one, two or three, relapse prevention was offered by the care manager by calling the patient every month and assessing anxiety symptoms with the BAI. Details of the program are reported elsewhere (Muntingh *et al.* 2009).

Care As Usual

The patients treated by GPs assigned to the Care As Usual condition could obtain any services normally available in the Netherlands. Every PCP could use the assistance of a psychiatric nurse. As the Care As Usual was operating as a control group, the GPs and psychiatric nurses did not receive additional training. The Dutch guideline of the treatment of anxiety disorders in primary care was accessible for all the GP's (Terluin *et al.* 2004). Although GPs were notified of the diagnosis of referred patients, they were not notified of the diagnosis and participation of screened patients. Patients in the Care As Usual group were all advised to seek treatment. After one year type of treatment delivered was assessed at the PCP by a research assistant using a checklist.

Data collection and outcome measures

The data was collected at 3-months intervals: Measurement took place at baseline (T0), three (T1), six (T2), nine (T9) and twelve (T4) months after inclusion. The self-report questionnaires were processed by blinded research assistants.

The aim of this economic evaluation was to assess the cost utility of Collaborative Stepped Care compared to Care As Usual. All relevant costs to society associated with the burden of anxiety disorders were taken into account: costs attributable to contacts with health providers, costs of medications (direct medical costs) and costs of productivity losses due to the anxiety disorder (productivity costs). Cost-utility was calculated by relating the difference in direct medical costs per patient receiving Collaborative Stepped Care or Care As Usual to the difference in terms of quality adjusted life years gained (cost-utility). This yielded a cost per QALY estimate. The analyses were also performed including productivity costs.

Cost measures

Medical costs

For calculating the total direct medical costs, the Trimbos/IMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) (Hakkaart-van Roijen, 2002) was used. The TiC-P measures utilisation of medical treatment such as the number of contacts with the GP and multiple other care providers (e.g. medical specialists and paramedics) during the last three months, as well as the medication used. The costs were estimated using the Dutch guidelines for cost calculations in health care (Oostenbrink *et al.* 2004). Reference unit prices from 2009 of the corresponding health care services were applied (Hakkaart-van Roijen *et al.* 2010). Unit costs per contact of the care manager were comparable to that of a nurse practitioner.

Productivity costs

For calculating productivity losses the Health and Labor questionnaire (SF-HQL) (van Roijen *et al.* 1996) was used. The SF-HLQ consists of three modules: absence from work, reduced efficiency at work and difficulties with job performance (van Dam *et al.* 1998). Productivity losses as measured by the SF-HLQ were valued over 4 weeks by using the "friction cost method" (Koopmanschap *et al.* 1995). This method takes into account the economic circumstances that limit the productivity lost to society.

Quality of life

The EuroQol (EQ-5D) (Cheung *et al.* 2009) generic health index is a standardised, patient-completed instrument which consists of five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated by the patient on three levels (no problems, some problems, and extreme problems). Thus, 243 (3^5) distinct health states are defined, each with a unique utility score, ranging from 1 (perfect health) to 0 ('death'). The health states were linked to empirical valuations of the Dutch general public, allowing utilities to be computed. To obtain one utility score, the patients mean utility scores were first linearly interpolated between utility scores over the study period. To calculate utility gain or loss the area-under-the curve method (AUC) was applied (Matthews *et al.* 1990).

Cost Utility analysis

An incremental cost-effectiveness ratio was calculated to calculate the costs per Quality Adjusted Life Year (QALY). The incremental cost-effectiveness ratio was calculated by dividing the incremental costs by the incremental effects.

Statistics

Analyses were conducted using the Statistical Package for the Social Sciences 19.0 (SPSS 19.0), Statistics and data (Stata 8.0 se) and Excel. First, the direct costs and quality of life scores were calculated by SPSS. No selective dropout was observed. The percentage of non-responders in the cost-data is shown in table 1.

Table 1: Pattern of non-response of participants (N=180) on the EQ5D and direct cost data at follow-up

Non-response	EQ5D	Direct Costs
After 3 months	15.6 %	15.6 %
After 6 months	26.7 %	26.7 %
After 9 months	26.1 %	26.1 %
After 12 months	25.6%	25.0 %

Missing values in direct costs and quality of life scores per time unit were modelled and imputed with chained equations (PMM) in Stata. Ten imputed datasets were created. Different baseline variables, like age and gender were included to get a better estimate. Propensity scores were used to correct for baseline differences between both groups. As our outcome measures differed from those in the effectiveness study of Muntingh and colleagues (2012), different confounders were used to balance our scores and propensity scores were again calculated. The uncertainty in the analysis was assessed using bootstrapping. This was expressed in a cost-effectiveness acceptability curve. The acceptability curve illustrates the probability that the cost-effectiveness ratio will be accepted for different cost limits.

Results

Table 2 summarises the baseline demographic and clinical patient characteristics for Care As Usual and Collaborative Stepped Care. In total 180 participants were included in the study (66 participants in the CAU group and 114 in the CSC group). At baseline, there was a significant difference between the groups on the BAI scores which affected QALY's gained, so propensity scores were calculated to compensate.

Direct medical costs

The total average direct medical costs were 1,854 Euro (95% confidence interval (CI) 1,726 to 1,986) for the Collaborative Stepped Care group, compared to 1,503 Euro (95 % CI 1,374 to 1,664) for the Care As Usual group. The average number of contacts and costs per health care provider are presented in Table 3. The percentage of costs are also presented in a pie chart, see Figure 2.

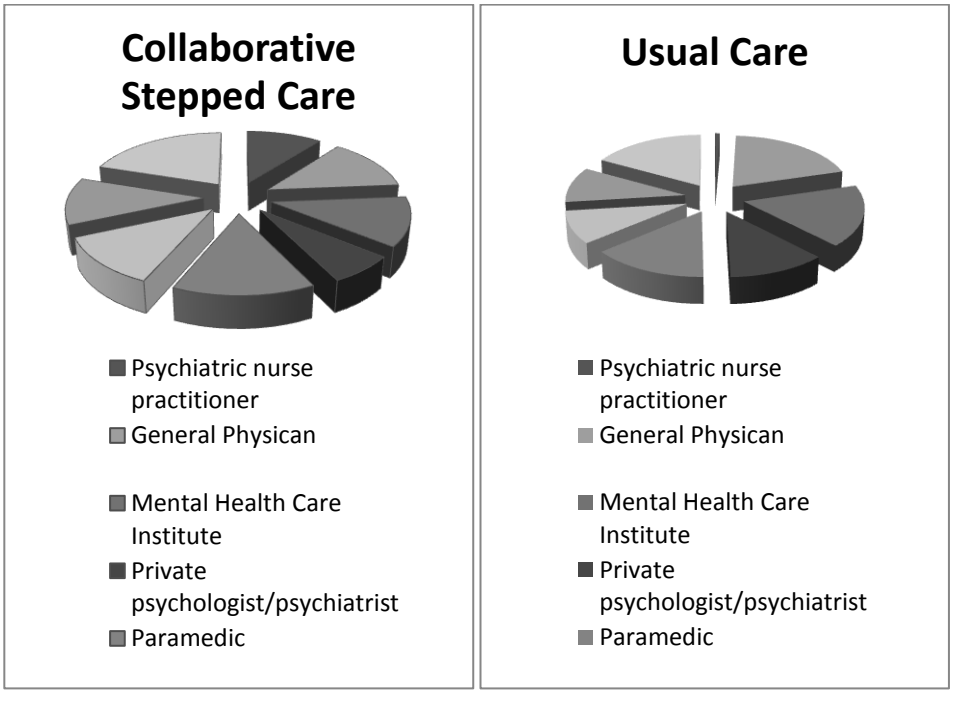

Figure 2: Percentage of costs from baseline to 12 months presented in a pie chart.

Table 2: Baseline demographic and clinical patient characteristics for Care As Usual and Collaborative Stepped Care

	Collaborative Stepped Care (N = 114)	**Care As Usual (N = 66)**	**Total (N = 180)**
Mean Age (SD)	44.98 (15.06)	49.08 (15.93)	46.48 (15.47)
Gender (% male)	31 (27.2 %)	26 (39.4 %)	57 (31.7 %)
Number of people with a paid job (%)	77 (67.5%)	41 (62.1 %)	118 (65.6 %)
Mean BAI Score * (SD)	24.59 (11.52)	20.04 (11.28)	22.09 (11.55)
Depression score (PHQ9), mean (SD)	9.40 (5.62)	8.98 (5.77)	9.25 (5.66)
EQ-5D, mean (SD)	0.61 (0.25)	0.65 (0.23)	0.64 (0.25)
Level of education			
Elementary school	10 (8.8%)	4 (6.2%)	14 (7.8%)
High school	68 (59.6%)	35 (53.8%)	103 (57.5%)
College	36 (31.6%)	26 (40.0%)	62 (34.6%)
Primary diagnosis			
PD	48 (42.1%)	29 (43.9%)	77 (42.8%)
GAD	32 (28.1%)	17 (25.8%)	49 (27.2%)
PD & GAD	34 (29.8%)	20 (30.3%)	54 (30.0%)
Co-morbid Depression			
Yes	34 (29.8%)	22 (33.3%)	56 (31.1%)
No	80 (70.2%)	44 (66.7%)	124 (68.9%)

*p<0.05

Table 3: Average number of contacts and costs by health care providers from baseline to 12 months (Euro´s, 2009).

	Collaborative Stepped Care [1]				Care As Usual [1]			
	Mean costs (SD)	% of total costs	Mean N° of contacts (SD)	% of patients using the service	Mean costs (SD)	% of total costs	Mean N° of contacts (SD)	% of patients using the service
Psychiatric nurse practitioner	177 (208)	11.8	2.3 (2.7)	50.0	9 (38)	0.7	0.1 (4,9)	6.1
Primary care physician	220 (209)	14.7	3.9 (3.7)	77.2	269 (246)	19.9	4.8 (4,4)	84.8
Mental Health Care Institute	203 (681)	13.5	1.2 (4.0)	14.9	235 (712)	17.3	1.4 (4,2)	13.6
Private psychologist/psychiatrist	114 (345)	7.6	1.3 (3.9)	16.7	164 (397)	12.1	1.9 (4,5)	25.8
Psychologist/Psychiatrist at outpatient centre of hospital	6 (36)	0.4	0.04 (0.2)	2.6	17 (100)	1.3	0.1 (0,6)	3.0
Occupational physician	20 (54)	1.3	0.4 (0.9)	15.8	29 (81)	2.1	0.5 (1,4)	15.2
Medical Specialist	56 (139)	3.7	1.3 (2.6)	36.8	51 (135)	3.8	1.7 (3,9)	40.9
Paramedic	234 (482)	15.6	6.5 (13.4)	41.2	195 (349)	14.4	5.4 (9,7)	43.9
Social Worker	15 (104)	1.0	0.2 (1.6)	2.6	26 (115)	1.9	0.4 (1,8)	7.6
Counselling centre for drugs alcohol	0 (0)	0.0	0.0 (0.0)	0.0	0 (0)	0.0	0.0 (0.0)	0.0
Alternative medicine	56 (160)	3.7	1.0 (2.9)	16.7	39 (91)	2.9	0.7 (1.7)	16.7
Selfhelp group	4 (24)	0.3	0.07 (0.5)	2.6	0 (0)	0.0	0.0 (0.0)	0.0
(parttime) day care	0 (0)	0	0.0 (0.0)	0.0	60 (461)	4.4	0.4(3.0)	1.5
(psychiatric) hospital days	199 (1,022)	13.3	0.4 (2.1)	6.1	125 (492)	9.2	0.3 (1.1)	7.6
Medication (general)	195 (832)	13.0	-	63.2	136 (199)	10.0	-	69.7

[1] The sum of the mean costs of health care providers is not equal to the average total costs. This is because multiple imputation was performed on the costs after calculating the total costs on different points in time.

Productivity costs

The indirect costs were €1,052 (SD=2,585) and €2,007 (SD=1,044) respectively for the Collaborative Stepped Care group and the Care As Usual group. Productivity cost due to absence from work were respectively €586 (SD=1,901) and €1,423 (SD=1,099) for the Collaborative Stepped Care group and the Care As Usual group. Costs caused by inefficiency at work were €611 (SD=1,552) and €677 (SD=1,330) for the Collaborative Stepped Care group and the Care As Usual group respectively.

Quality of life

Quality of life scores were imputed. The overall improvement in quality of life over time was calculated by the Area Under the Curve method. After imputation, outcome variables were corrected, using propensity scores and bootstrapping, which did bring more balance in our baseline scores on quality of life. A balance table was generated, see Table 4. Quality of life scores are shown in Table 5. The difference in improvement between both groups of 0.05 QALY's was significant over time (95% CI 0.04 to 0.07, p<0.01).

Table 4: Balance table for the EQ5D at baseline

	Collaborative Stepped Care	Care As Usual
Baseline before propensity scores	0.61 (SD=0.25)	0.65 (SD=0.23)
Baseline after propensity scores	0.62 (SD=0.24)	0.60 (SD=0.25)

Table 5: Mean Utility scores (SD) by treatment arm at baseline, after 3 months, after 6 months and after 1 year.

	Collaborative Stepped Care	Care As Usual
Baseline	0.62 (SD=0.24)	0.60 (SD=0.25)
After 3 months	0.71 (SD=0.22)	0.65 (SD=0.23)
After 6 months	0.73 (SD=0.24)	0.64 (SD=0.26)
After 9 months	0.73 (SD=0.24)	0.72 (SD=0.25)
After 1 year	0.80 (SD=0.19)	0.73 (SD=0.29)

Cost Utility Analysis

The average quality of life years (QALY's) gained was higher in the Collaborative Stepped Care group. The direct medical costs were also higher in the Collaborative Stepped Care group, leading to an incremental cost-effectiveness ratio (ICER) of €6,385 per QALY, see Table 6.

Table 6. The mean direct medical costs, QALY's gained (incremental utility), and the incremental costs per QALY (ICER)

	Collaborative Stepped Care (n=114)	**Care As Usual (n=66)**
Average direct medical costs	€ 1,854 (95% CI 1,726 to 1,986)	€ 1,503 (95% CI 1,374 to 1,664)
Incremental utility	0.05 (95% CI 0.04 to 0.07)	
ICER	6,385	

We first explored the incremental cost utility for the direct costs. The incremental cost-effect ratio (100%) falls in the northeast quadrant of the incremental cost-effectiveness plane, demonstrating that Collaborative Stepped Care is more costly but also more effective than the Care As Usual. Another way to present the uncertainty in the data is the acceptability curve shown in Figure 3.

For example, at a threshold of 20,000 Euro/QALY the probability that the ratio is acceptable is more than 90%. From this figure, we may also conclude that, taking uncertainty into account, Collaborative Stepped Care is cost effective.

Including productivity costs did change our result as Collaborative Stepped Care became dominant, meaning that it was less costly and more effective compared to Care As Usual. The ratio decreased to -4,977 Euro/Qaly. The majority (91%) of the incremental cost-effect ratio now fell into the southeast quadrant demonstrating that collaborative care was dominant. At a threshold of 20,000 Euro/QALY the probability that the ratio is acceptable is 100 %, see Figure 4.

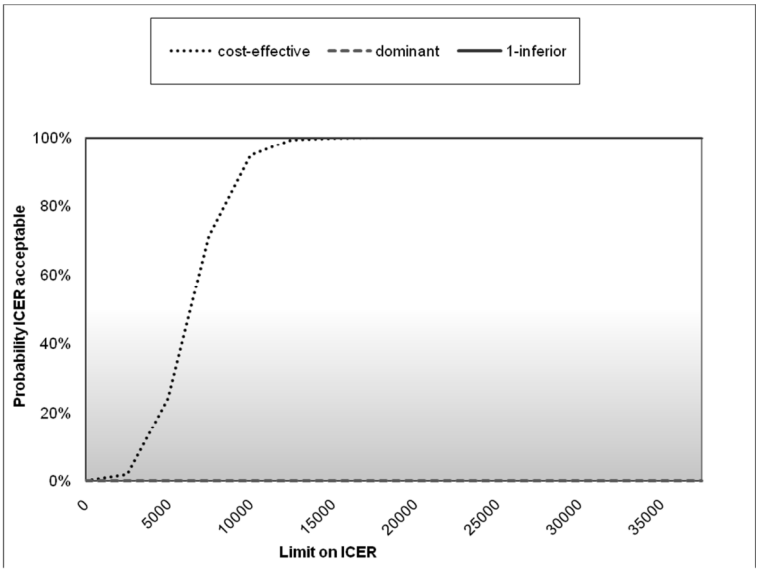

Figure 3. Acceptability curve for the direct costs of Collaborative Stepped Care.

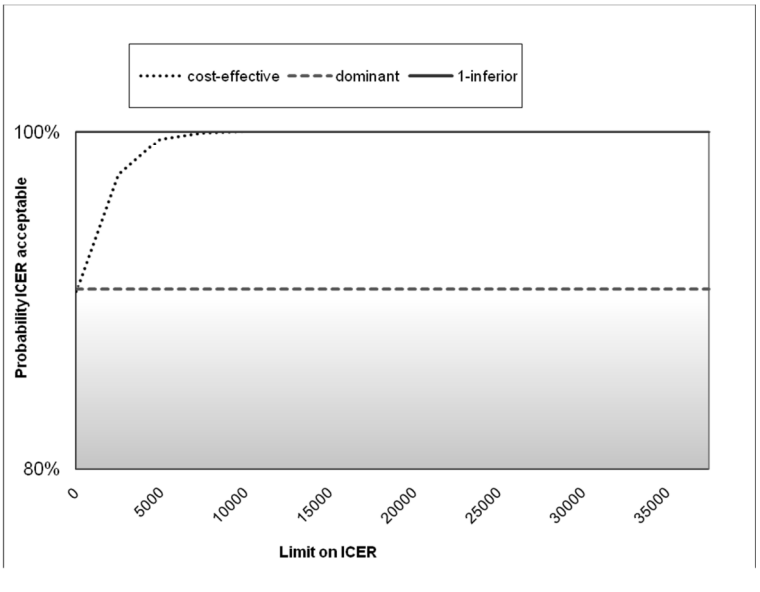

Figure 4. Acceptability curve for the direct and indirect costs of Collaborative Stepped Care.

Conclusion

This study is the first cost-utility analysis comparing Collaborative Stepped Care to Care As Usual for anxiety disorders and shows that Collaborative Stepped Care is a highly cost-effective intervention. This study showed that the cost per QALY from a health care perspective was 6,385 Euro/QALY. Including productivity costs (societal perspective) decreased the ratio to -4,977 Euro/Qaly.

According to the Council for Public and Health Care (RVZ) the threshold in relation to the acceptability of the treatment has to depend on the severity of disease with a maximum Incremental Cost-effectiveness Ratio (ICER) of 80,000 Euro/QALY. In our study, the uncertainty in the ICER was very low; at a threshold of 20,000 Euro/QALY the probability that the ICER would be accepted was almost 90% and even 100% when including productivity costs. Hence, treating patients with generalised anxiety or panic disorder in primary care applying Collaborative Stepped Care is a highly cost-effective intervention.

The differences in medical costs are mainly due to the higher costs of the care manager in the collaborative care group compared to the Care As Usual group. Paramedic costs were high for both groups showing that besides mental health care, somatic care is frequently used (Koopmans & Lamers, 2006). Medical costs of Collaborative Stepped Care were comparable to those of guideline concordant care for patients with anxiety or depressive disorders (Prins *et al.* 2011). Including the productivity costs did change our results as the costs for absence at work were higher in the Care As Usual group. This finding supports the research of Krol and colleagues (2011) and Smit and colleagues (2006), as productivity costs had a considerable effect on our outcomes.

Over time, the quality of life improved more in the Collaborative Stepped Care group when compared to the Care As Usual group. In the Care As Usual group quality of life declined slightly after 9 months, indicating that Collaborative Stepped Care may have a more prolonged effect on the quality of life. In addition, the quality of life improved more rapidly in the intervention group. This may be due to the effectiveness of guided self-help that was administered in the first step of the treatment.

This study produced results which corroborate the findings of Katon and colleagues (2006) and Joesch and colleagues (2011) that the costs of collaborative care were higher and the effects were larger compared to care as usual for Panic Disorder. However, the findings of the current study do not fully support the previous research of Katon and colleagues (2002) which showed that collaborative care was dominant compared to care as usual from a health care perspective (only including medical costs). In our study, collaborative care was only dominant when including productivity costs. However, the intervention applied in the study of Katon and colleagues (2002) was different from our collaborative care intervention; a brief Psychiatric intervention was used in the intervention group that consisted of approximately 2 sessions per patient which was less than the approximately 6 sessions per patient in our intervention. In addition, there was no care manager involved in the study of Katon and colleagues (2002), who was responsible for the largest part of the additional costs in our study. None of the previous collaborative care studies used a stepped component in collaborative care. Furthermore, all previous studies were North American and since there are important differences between European and North American health care systems, these studies cannot be generalised without consideration.

In the article of Bower and Gilbody (2005), it was suggested that Collaborative Stepped Care may cost less because of lower resource use. However, in the present study resource use of both groups was comparable. At baseline, also patients who already received some (≤2 sessions per month) psychological or psychiatric treatment were included, so patients from the Care As Usual group and Collaborative Stepped Care were already equal in terms of resource use of these mental health care services. Despite the lack of difference concerning resource use, Collaborative Stepped Care was still cost-effective, due to the substantial influence that treatment had on quality of life.

The study was conducted in a naturalised setting, which involved GPs selecting the patients. There was a selection bias for two reasons. Firstly, the GPs in the Care As Usual group had a preference for the collaborative care group and they had difficulties selecting patients for the Care As Usual group. Secondly, the GPs in the Collaborative Stepped Care intervention received training, which might have contributed to their

improved ability to detect patients. To minimise selection bias after this initial selection, all patients followed the same procedure with a diagnostic interview conducted by a researcher who was blind for randomisation status. After selection patients were obliged to accept the assigned treatment. However, there were still more patients in the Collaborative Stepped Care group (N=114) than in the Care As Usual group (N=66). This study used cluster randomisation, which was necessary because otherwise the usual care would have been more restricted as the GP would not have the opportunity to send patients to a psychiatric nurse or psychologist because this professional was trained in the new intervention. In this way, the usual care would be restricted to prescription of medication or referral to secondary care.

Based on age, gender, PHQ-score, EQ5D-score, level of education, primary diagnosis and comorbidity, the Care As Usual and the Collaborative Stepped Care group were comparable. They were not comparable with respect to their BAI score, so propensity scores were used to correct.

Although Collaborative Stepped Care was cost-effective compared to Care As Usual, the results of this study leave room for improvement (Muntingh *et al.* 2012). Most importantly, not all the elements of stepped care approach were sufficiently implemented (Muntingh *et al.* 2012). There was a relatively large proportion of patients (36%) in the Collaborative Stepped Care group that did not want to continue treatment after step 1 (Muntingh *et al.* 2012). An explanation for this high rate of patients discontinuing after step 1 is that patients felt that they were sufficiently empowered to cope with their anxiety problems, although they did not achieve criteria for remission. As Scogin and colleagues (2003) already pointed out, research is needed to investigate if unsuccessfully treated patients with initial lower intensity treatments will be less willing to undergo further, more intensive treatment. The implementation of Collaborative Stepped Care may be further improved by increasing the case load of care managers, adjusting follow-up procedures to fit into the daily tasks of the care manager and improving medication prescription and adherence by a greater role of the care manager and the psychiatrist in medication management.

Despite some of these limitations, the findings of this study suggest a high cost-effectiveness for Collaborative Stepped Care for anxiety disorders. From a societal perspective, Collaborative Stepped Care even becomes dominant. In combination

with the effectiveness study (Muntingh *et al.* 2012), this finding highly supports the implementation of Collaborative Stepped Care in daily practice and widespread implementation is therefore justified.

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REFERENCES

Andlin-Sobocki, P., & Wittchen, H. U. (2002). Cost of anxiety disorders in europe. *Journal of Clinical Psychiatry,* **12**(1), 39-44.

Bakker, I. M., van Marwijk, H. W., Terluin, B., Anema, J. R., van Mechelen, W., & Stalman, W. A. (2010). Training GP's to use a minimal intervention for stress-related mental disorders with sick leave (MISS): Effects on performance: Results of the MISS project; a cluster-randomised controlled trial [ISRCTN43779641. *Patient Education and Counseling,* **78**(2), 206-211.

Barrera, T. L., & Norton, P. J. (2009). Quality of life impairment in generalized anxiety disorder, social phobia, and panic disorder. *Journal of Anxiety Disorders,* **23**(8), 1086-1090.

Beard, C., Weisberg, R. B., & Keller, M. B. (2010). Health-related quality of life across the anxiety disorders: Findings from a sample of primary care patients. *Journal of Anxiety Disorders,* **24**(6), 559-564.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology,* **56**(6), 893-897.

Bereza, B. G., Machado, M., & Einarson, T. R. (2009). Systematic review and quality assessment of economic evaluations and quality-of-life studies related to generalized anxiety disorder. *Clinical Therapeutics,* **31**(6), 1279-1308.

Bower, P., & Gilbody, S. (2005). Stepped care in psychological therapies: Access, effectiveness and efficiency. narrative literature review. *The British Journal of Psychiatry : The Journal of Mental Science,* **186**, 11-17.

Cheung, K., Oemar, M., Oppe, M., & Rabin, R. (2009). *Eq-5D user guide, basic information on how to use EQ-5D*EuroQol Group.

Fernandez, A., Haro, J. M., Martinez-Alonso, M., Demyttenaere, K., Brugha, T. S., Autonell, J., et al. (2007). Treatment adequacy for anxiety and depressive disorders in six european countries. *The British Journal of Psychiatry : The Journal of Mental Science,* **190**, 172-173.

Hakkaart-van Roijen, L. (2002). *Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in dutch).* Rotterdam: Institute for Medical Technology Assessment.

Hakkaart-van Roijen, L., Tan, S. S., & Bouwmans, C. A. M. (2010). Handleiding voor kostenonderzoek : Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Diemen: College voor zorgverzekeringen.

Heuzenroeder, L., Donnelly, M., Haby, M. M., Mihalopoulos, C., Rossell, R., Carter, R., et al. (2004). Cost-effectiveness of psychological and pharmacological interventions for generalized anxiety disorder and panic disorder. The Australian and New Zealand Journal of Psychiatry, **38**(8), 602-612.

Jacob, V., Chattopadhyay, S. K., Sipe, T. A., Thota, A. B., Byard, G. J., Chapman, D. P., et al. (2012). Economics of collaborative care for management of depressive disorders: A community guide systematic review. *American Journal of Preventive Medicine,* **42**(5), 539-549.

Joesch, J. M., Sherbourne, C. D., Sullivan, G., Stein, M. B., Craske, M. G., & Roy-Byrne, P. (2011). Incremental benefits and cost of coordinated anxiety learning and management for anxiety treatment in primary care. *Psychological Medicine,* 1-12.

Katon, W., Russo, J., Sherbourne, C., Stein, M. B., Craske, M., Fan, M. Y., et al. (2006). Incremental cost-effectiveness of a collaborative care intervention for panic disorder. *Psychological Medicine,* **36**(3), 353-363.

Katon, W., Von Korff, M., Lin, E., & Simon, G. (2001). Rethinking practitioner roles in chronic illness: The specialist, primary care physician, and the practice nurse. *General Hospital Psychiatry,* **23**(3), 138-144.

Katon, W. J., Roy-Byrne, P., Russo, J., & Cowley, D. (2002). Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. *Archives of General Psychiatry,* **59** (12), 1098-1104.

Koopmans, G. T., & Lamers, L. M. (2006). Is the impact of depressive complaints on the use of general health care services dependent on severity of somatic morbidity? *Journal of Psychosomatic Research,* **61**(1), 41-50.

Koopmanschap, M. A., Rutten, F. F., van Ineveld, B. M. & van Roijen, L. (1995). The friction cost method for measuring indirect costs of disease. *J Health Econ.* **14**, 171-189.

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O., & Lowe, B. (2007). Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. *Annals of Internal Medicine,* **146** (5), 317-325.

Krol, M., Papenburg, J., Koopmanschap, M., & Brouwer, W. (2011). Do productivity costs matter?: The impact of including productivity costs on the incremental costs of interventions targeted at depressive disorders. *PharmacoEconomics,* **29** (7), 601-619.

Lieb, R., Becker, E., & Altamura, C. (2005). The epidemiology of generalized anxiety disorder in europe. *European Neuropsychopharmacology,* **15**, 445-452.

Matthews, J. N. S., Altman, D. G., Campbell, M. J., & Royston, P. (1990). Analysis of serial measurements in medical research. *British Medical Journal,* **300**, 230-235.

Muntingh, A. D. T., van der Feltz-Cornelis, C. M., van Marwijk, H. W. J., Spinhoven, P., Assendelft, W. J. J., de Waal, , M.W.M., et al. (2012). Effectiveness of collaborative stepped care for anxiety disorders in primary care: A pragmatic cluster randomised controlled trial. *Submitted for publication.*

Muntingh, A. D., van der Feltz-Cornelis, C. M., van Marwijk, H. W., Spinhoven, P., Assendelft, W. J., de Waal, M. W., et al. (2009). Collaborative stepped care for anxiety disorders in primary care: Aims and design of a randomized controlled trial. *BMC Health Services Research,* **9**, 159.

Nadiga, D. N., Hensley, P. L., & Uhlenhuth, E. H. (2003). Review of the long-term effectiveness of cognitive behavioral therapy compared to medications in panic disorder. *Depression and Anxiety, 17*(2), 58-64.

Olatunji, B. O., Cisler, J. M., & Tolin, D. F. (2007). Quality of life in the anxiety disorders: A meta-analytic review. *Clinical Psychology Review,* **27** (5), 572-581.

Oostenbrink, J. B., Bouwmans, C. A. M., & Koopmanschap, M. A. (2004). *Handleiding voor kostenonderzoek, methoden en standaardkostprijzen voor economische evaluaties in de gezondheidszorg (manual for research on costs, methods and standardized cost prices for economic evaluation in health care).* Health Care Insurance Board (College voor zorgverzekeringen),.

Prins, M., Bosmans, J., Verhaak, P., van der Meer, K., van Tulder, M., van Marwijk, H., et al. (2011). The costs of guideline-concordant care and of care according to patients' needs in anxiety and depression. *Journal of Evaluation in Clinical Practice,* **17**(4), 537-546.

Prins, M. A., Verhaak, P. F., van der Meer, K., Penninx, B. W., & Bensing, J. M. (2009). Primary care patients with anxiety and depression: Need for care from the patient's perspective. *Journal of Affective Disorders,* **119** (1-3), 163-171.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., et al. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Archives of General Psychiatry,* **62** (12), 1332-1341.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., et al. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. *JAMA : The Journal of the American Medical Association,* **303** (19), 1921-1928.

Roy-Byrne, P. P., Wagner, A. W., & Schraufnagel, T. J. (2005a). Understanding and treating panic disorder in the primary care setting. *The Journal of Clinical Psychiatry, 66 Suppl 4*, 16-22.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., et al. (2005b). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Archives of General Psychiatry,* **62** (3), 290-298.

Roy-Byrne, P. P., & Wagner, A. (2004). Primary care perspectives on generalized anxiety disorder. *The Journal of Clinical Psychiatry,* **65** *Suppl 13*, 20-26.

Roy-Byrne, P., Russo, J., Dugdale, D. C., Lessler, D., Cowley, D., & Katon, W. (2002). Undertreatment of panic disorder in primary care: Role of patient and physician characteristics. *The Journal of the American Board of Family Practice / American Board of Family Practice,* **15** (6), 443-450.

Roy-Byrne, P. P., Katon, W., Cowley, D. S., & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Archives of General Psychiatry, 58*(9), 869-876.

Scogin, F. R., Hanson, A., & Welsh, D. (2003). Self-administered treatment in stepped-care models of depression treatment. *Journal of Clinical Psychology,* **59** (3), 341-349.

Smit, F., Cuijpers, P., Oostenbrink, J., Batelaan, N., de Graaf, R., & Beekman, A. (2006). Costs of nine common mental disorders: Implications for curative and preventive psychiatry. *The Journal of Mental Health Policy and Economics,* **9** (4), 193-200.

Smolders, M., Laurant, M., Roberge, P., van Balkom, A., van Rijswijk, E., Bower, P., et al. (2008). Knowledge transfer and improvement of primary and ambulatory care for patients with anxiety. *Canadian Journal of Psychiatry.Revue Canadienne De Psychiatrie,* **53** (5), 277-293.

Spitzer, R. L., Kroenke, K., & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. primary care evaluation of mental disorders. patient health questionnaire. *JAMA : The Journal of the American Medical Association,* **282** (18), 1737-1744.

Stein, M. B., Roy-Byrne, P. P., Craske, M. G., Campbell-Sills, L., Lang, A. J., Golinelli, D., et al. (2011). Quality of and patient satisfaction with primary health care for anxiety disorders. *The Journal of Clinical Psychiatry,* **72** (7), 970-976.

Stein, M. B., Sherbourne, C. D., Craske, M. G., Means-Christensen, A., Bystritsky, A., Katon, W., et al. (2004). Quality of care for primary care patients with anxiety disorders. *The American Journal of Psychiatry,* **161** (12), 2230-2237.

Terluin, B., Van Heest, F. B., Van der Meer, K., Neomagus, G. J. H., Hekman, J., Aulbers, L. P. J., et al. (2004). NHG-standaard angststoornissen. *Huisarts En Wetenschap,* **47** (1), 26-37.

van Dam, Q. D., Spijker, A., Arends, L. R., Hakkaart-Roijen, L., Donker.M.C.H. & Trijsburg, R.W. (1998). Costeffectiveness of psychotherapy: A feasiblity study (in Dutch). *J Pychotherapy* **24**, 5-22.

van Boeijen, C. A., van Oppen, P., van Balkom, A. J., Visser, S., Kempe, P. T., Blankenstein, N., et al. (2005). Treatment of anxiety disorders in primary care practice: A randomised controlled trial. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners,* **55** (519), 763-769.

van Roijen, L., Essink-Bot, M. L., Koopmanschap, M. A., Bonsel, G., & Rutten, F. F. (1996). Labor and health status in economic evaluation of health care. the health and labor questionnaire. *International Journal of Technology Assessment in Health Care,* **12**, 405-415.

van Schaik, D. J., Klijn, A. F., van Hout, H. P., van Marwijk, H. W., Beekman, A. T., de Haan, M., et al. (2004). Patients' preferences in the treatment of depressive disorder in primary care. *General Hospital Psychiatry,* **26** (3), 184-189.

van Steenbergen-Weijenburg, K. M., van der Feltz-Cornelis, C. M., Horn, E. K., van Marwijk, H. W., Beekman, A. T., Rutten, F. F., et al. (2010). Cost-effectiveness of collaborative care for the treatment of major depressive disorder in primary care. A systematic review. *BMC Health Services Research,* **10**, 19.

van Vliet, I. M., Leroy, H., & van Megen, H. J. M. (2007). De MINI-internationaal neuropsychiatrisch interview: Een kort gestructureerd diagnostisch interview voor DSM-IV en ICD-10 psychiatrische stoornissen. *Tijdschrift Voor Psychiatrie,* **49**

Walters, K., Buszewicz, M., Weich, S., & King, M. (2008). Help-seeking preferences for psychological distress in primary care: Effect of current mental state. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners,* **58** (555), 694-698.

Chapter 5

Study a

Screening high risk patients and assisting in diagnosing anxiety in primary care: The Patient Health Questionnaire evaluated

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Abstract

Background: Questionnaires may help detection and diagnosis of anxiety disorders in primary care. However, utility of these questionnaires in target populations is rarely studied. Therefore the Patient Health Questionnaire anxiety modules (PHQ) were evaluated for use as: a) a screener in high risk patients, and/or b) a case-finder for general practitioners (GPs) to detect anxiety disorders.

Methods: A cross-sectional analysis was performed, embedded in a cluster randomised controlled trial with 43 participating primary care practices in the Netherlands. The validity of the PHQ was assessed in two separate samples: 1) 170 patients at risk for (developing) anxiety disorders according to their electronic medical records (high risk sample), 2) 141 patients identified as a possible 'anxiety case' by a GP (GP-identified sample). All patients completed the PHQ and were interviewed with the MINI International Neuropsychiatric Interview to classify DSM-IV anxiety disorders. Psychometric properties were calculated, and a logistic regression analysis was performed to assess the diagnostic value of the PHQ.

Results: Using only the screening questions of the PHQ, the positive predictive value (PPV) was 76% and the negative predictive value (NPV) was 88% in the high risk sample. A positive PHQ score significantly increased the odds of an anxiety disorder diagnosis in high risk patients (odds ratio=23.4; 95% confidence interval 6.9 to 78.8). In GP-identified patients the official algorithm showed the best characteristics with a PPV of 96%, a NPV of 38% and an odds ratio of 13.9 (95% confidence interval 3.8 to 50.6).

Conclusions: The PHQ may be used to screen for anxiety disorders in high risk primary care patients and to confirm a preliminary anxiety disorder diagnosis made by a GP, but not for ruling out the presence of an anxiety disorder in GP-identified patients.

Background

In health care systems in which the general practitioner (GP) acts as the gatekeeper to mental health care, GPs ability to accurately detect and diagnose psychiatric disorders is crucial. Anxiety disorders are a major category of the psychiatric disorders encountered in primary care (Kessler *et al.* 2010). The ability of GPs to detect anxiety disorders has often been criticised (Kessler *et al.* 2002) as GPs only detect one third to one half of the patients with an anxiety disorder (Ormel *et al.* 1990; Wittchen *et al.* 2002; Smolders *et al.* 2009). Although GPs do suspect psychological problems in many of these patients, they do not often classify these problems with a diagnosis of an anxiety disorder (Janssen *et al.* 2012). However, the classification of an anxiety disorder diagnosis facilitates the implementation of clinical guidelines, as these include diagnosis specific treatments (Smolders *et al.* 2009; National Institute for Health and Clinical Excellence 2011). Furthermore, the provision of multidisciplinary care may be enhanced by the use of common terms by GPs and mental health professionals (Gunn *et al.* 2010; Franx *et al.* 2012).

To improve the identification of patients with anxiety disorders in primary care patients, screening is often considered (Buszewicz & Chew-Graham 2011). However, as screening large populations of patients is not considered feasible, purposeful screening of patients who are at high risk of developing a disorder has been proposed as an alternative (Christensen & Olesen 2005). As low-intensity treatments become increasingly available in primary care (Richards 2012) and through the internet (Andrews *et al.* 2010), this may open doors for the successful implementation of selective screening programs. Furthermore, a screening questionnaire might help GPs to distinguish psychological problems from an anxiety disorder (Tiemens *et al.* 1999). Patients appreciate the assessment of symptoms as part of the diagnostic process and GPs additionally use the questionnaire to explain the diagnosis to patients (Dowrick *et al.* 2009). However, the practical use of screening questionnaires, such as screening in high risk groups (selective screening) and assisting in diagnosing an anxiety disorder, are rarely studied. We chose to investigate the performance of the Patient Health Questionnaire (PHQ), because this scale was specifically designed for use in primary care (Spitzer *et al.* 1999) and has shown adequate psychometric properties (Spitzer *et al.*

1999; Diez-Quevedo *et al.* 2001; Persoons *et al.* 2003). The PHQ consists of different modules about common mental health disorders, including a module about panic disorder and one about general anxiety. Earlier studies about the PHQ anxiety module focused on the validity as a screener in a random primary care sample (Spitzer *et al.* 1999), different groups of hospital patients (Spitzer *et al.* 2000; Diez-Quevedo *et al.* 2001; Persoons *et al.* 2003), the community (Eack *et al.* 2006) and in psychosomatic outpatients (Lowe *et al.* 2003). A recent study showed that the ability of the PHQ panic module to detect panic disorder in high risk primary care patients was moderate (Wittkampf *et al.* 2010). However, most GPs will be interested in the presence of any anxiety disorder, where after they may decide to perform extra diagnostic procedures or to refer the patient to a mental health professional. Therefore, we evaluated the PHQ anxiety modules for use as: a) a screener in high risk patients, and/or b) a case-finder for general practitioners (GPs) to detect anxiety disorders.

Method

Participants

The present study was embedded in a cluster randomised controlled trial (RCT), focusing on the treatment of panic disorder and generalised anxiety disorder in primary care (Muntingh *et al.* 2009). Patients were recruited between November 2008 and March 2010 in the 43 primary care practices participating in the RCT. Two groups of patients were studied: 1) primary care patients at risk for (developing) anxiety disorders, identified from their electronic medical record (high risk sample); 2) patients identified as a possible 'anxiety case' by their GP (GP-identified sample).

Exclusion criteria

Excluded were patients who were suicidal, patients who suffered from dementia or other severe cognitive disorders, psychotic disorder, bipolar disorder, dependence on drugs or alcohol, and patients who were in an unstable severe medical condition as diagnosed by their GP. Other exclusion criteria were insufficient knowledge of the Dutch language to complete the questionnaire and receiving regular psychological treatment.

Selection of the high risk sample

To select patients who were at risk for (developing) anxiety disorders, electronic medical records (EMR) were searched. Of the 43 practices participating in the RCT, 24 practices agreed to the screening procedure and did have an electronic system suitable for selecting patients from the EMR. Patients were selected from the EMR if they were over 18 years of age and had visited their general practitioner in the past three months with symptoms that were considered to indicate a high risk for anxiety disorders. Such symptoms were fatigue, headache, dizziness, weakness, muscle- and joint pain, stomach ache, chest pain, hyperventilation, (symptoms of) anxiety or depression, or social problems (such as loneliness or marital problems). These symptoms have been identified as risk factors for having or developing anxiety disorders (Kroenke et al. 1994; Karsten et al. 2011; Flensborg-Madsen et al. 2012).

Selection of the GP-identified sample

GPs were asked to identify patients with an anxiety disorder (specifically panic disorder and generalised anxiety disorder) for participation in the RCT. GPs (N=37) who were allocated to the intervention group of the RCT attended a 3-hour workshop on the diagnosis and treatment of anxiety disorders. GPs in the control group (N=26) of the RCT received an educational folder with instructions on how to diagnose patients with an anxiety disorder (specifically panic disorder and generalised anxiety disorder).

Procedure

Patients who were selected from the EMR (high risk sample) and patients who were identified by their GP (GP-identified sample) received a letter informing them about the RCT, together with an informed consent form and the Patient Health Questionnaire (PHQ) anxiety module. The patients were asked to return the PHQ and the informed consent form directly to the researcher. They were not informed about the allocation of their GP in the RCT. Patients who gave informed consent were contacted by telephone by a research assistant to perform a diagnostic interview.

Measures

Screener

The PHQ anxiety modules (Spitzer *et al.* 1999) consist of 22 questions concerning anxiety symptoms experienced during the past four weeks. The first 15 questions screen for a panic disorder, starting with four questions about the presence of panic attacks and anxiety (e.g. "In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?") and subsequently asking about symptoms of panic attacks, such as "Were you short of breath?". The second part of the PHQ consists of 7 characteristics of generalised anxiety, starting with a screening question "Feeling nervous, anxious, on edge, or worrying a lot about different things", followed by symptoms of generalised anxiety. The respondents are asked to indicate how often they were bothered by these problems ("not at all", "several days" or "more than half the days"). Good overall accuracy has been reported for both sub-scales (Spitzer *et al.* 1999; Diez-Quevedo *et al.* 2001; Lowe *et al.* 2003). To screen positive on the panic module, the first four questions should be answered affirmatively, and at least four symptoms of panic attacks should be present. To screen positive for any anxiety disorder/generalised anxiety disorder, the first question should be answered with "more than half the days" and at least three symptoms of generalised anxiety should be present more than half the days (Spitzer *et al.* 1999). A positive score on one of the sub-scales was counted as a positive PHQ score. We also tested the diagnostic validity of the two screening questions, because the use of this simplified algorithm may be better suitable for high risk groups (Wittkampf *et al.* 2010) and is attractive for use in busy general practices. A confirmative answer on one of the two screening questions was counted as a positive PHQ screening score ("In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?" and "Feeling nervous, anxious, on edge, or worrying a lot about different things - more than half the days").

Reference standard

The Mini International Neuropsychiatric interview (MINI-PLUS) was used as a reference standard. The MINI-PLUS is a short structured diagnostic interview that is used to determine the most common DSM-IV (American Psychiatric Association 2001) and ICD-10 (World Health Organisation 1993) psychiatric disorders (Sheehan

et al. 1998)(Dutch version (van Vliet et al. 2000)). The following anxiety disorders were classified: panic disorder (PD) with or without agoraphobia, generalised anxiety disorder (GAD), social phobia, simple phobia, obsessive compulsive disorder, post traumatic stress disorder and agoraphobia (without panic disorder). The interviewers who conducted the MINI interviews by telephone had a medical or psychological background, with degrees varying from undergraduate to master. They received training in how to carry out the MINI interview and were supervised by a psychologist and a psychiatrist. At least two interviews carried out by each interviewer were audio-taped and evaluated by the psychologist. All interviewers were blinded for the PHQ score to prevent confirmation bias.

Recruitment

High risk sample

The PHQ was sent to 2,408 patients who were at risk for developing an anxiety disorder according to the information in their EMR. A total of 786 (32.6%) patients completed and returned the questionnaire (Figure 1). The proportion of females did not differ significantly between responders and non-responders (70% versus 69%, $p>0.05$) but the responders were slightly older than the non-responders (51.9 versus 48.3 years, $p < .05$). All screen-positive patients (N=150) and a random selection of 57 screen-negative patients were invited for a MINI interview. After the exclusion of patients who met exclusion criteria (N=13, 8.7% screen-positives, N=1, 2% screen-negatives), and because of non-response (N=16, 10.7% screen-positives, N=7, 10.5% screen-negatives), 121 screen-positive participants and 49 screen-negative participants had a MINI interview (n=170). Figure 1 presents a flowchart of the high risk sample.

GP-identified sample

GPs of 37 practices selected 207 patients for the study. All patients who gave informed consent and who did not meet the exclusion criteria (N=164, 79.2%) were invited for a MINI interview, irrespective of their PHQ score, and eventually 141 patients were interviewed. Figure 2 presents a flowchart of patients identified by their GP.

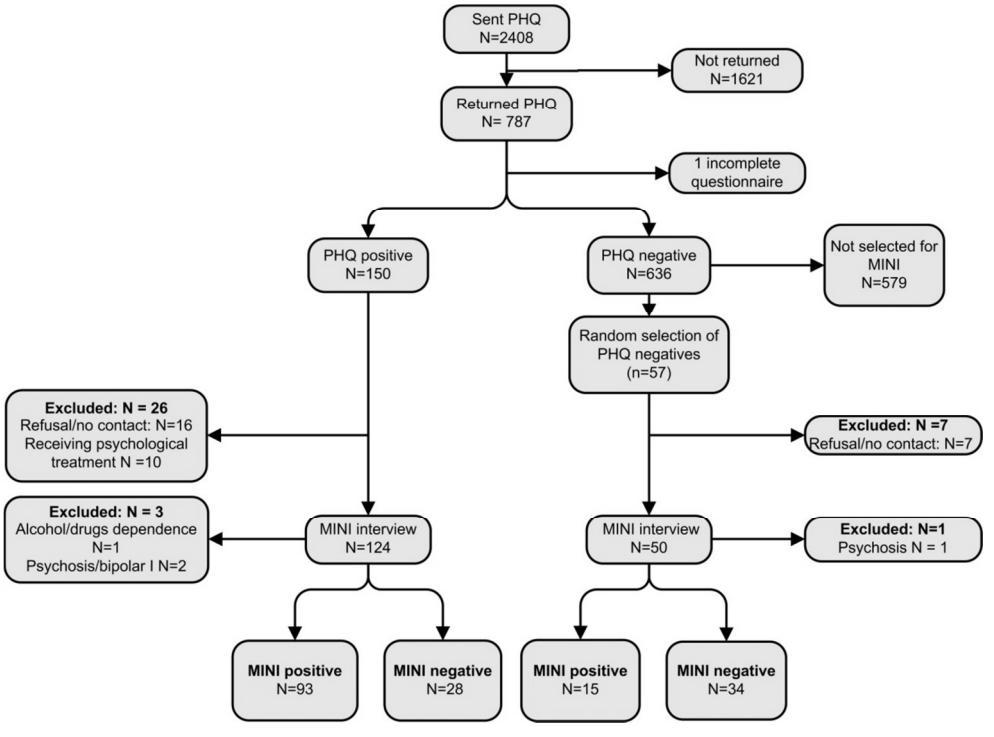

Figure 1. Flowchart of participants at risk for (developing) an anxiety disorder according to their electronic medical record (high risk sample)

Data analysis

In the high risk sample, we had to correct for the fact that we included a random sample of screen negatives, while we did include all screen positives. Such a selection procedure creates an imbalance that influences the prevalence and thus the test characteristics. Weights were used to transform the sample back to the original distribution of screen positives and screen negatives (Pepe 2003). A screen-positive patient received a weight of 0.27 (150/121*170/786) and a screen-negative patient received a weight of 2.81 (636/49*170/786). A similar procedure was followed for the analysis in the high risk sample using the two screening questions. All psychometric analyses concerning the high risk group were performed on the weighted sample. The following indicators of criterion validity were calculated: positive predictive value, negative predictive value, sensitivity, specificity, overall accuracy and receiver

operating characteristics (area under the curve, AUC) (Fischer *et al.* 2003). The MINI classification functioned as reference standard for the diagnosis of an anxiety disorder. A multilevel logistic regression analysis was performed to determine whether a positive PHQ score increased the odds of a MINI anxiety disorder classification. SPSS version 15.0 (SPSS Inc. 2006) was used for most statistical analyses; MLwiN V2 2.21 (Rasbash *et al.* 2011) was used for the multilevel logistic regression analysis.

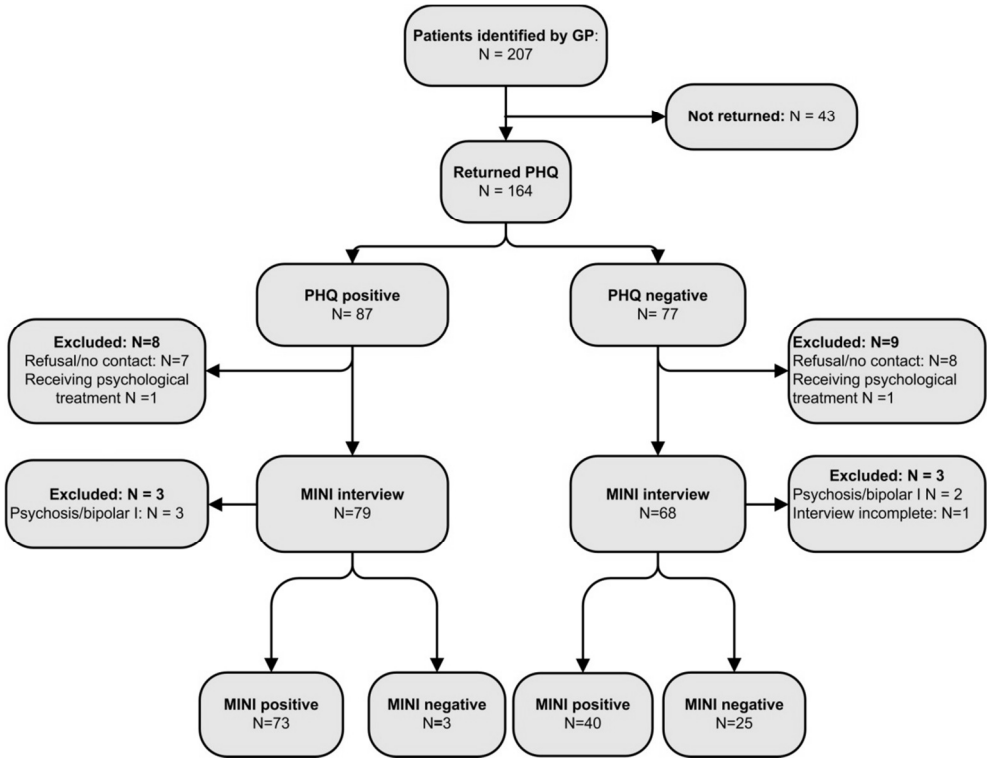

Figure 2: Flowchart of patients identified as a case by GPs (GP-identified sample)

Results

Participants

In the (weighted) high risk sample (N=170) the mean age was 54.6 (SD 13.2), the percentage of females was 74% and the prevalence of any anxiety disorder was 39%. In the GP-identified sample (N=141) the mean age was 47.5 (SD 16.4), the percentage of females was 71% and the prevalence of any anxiety disorder was 80% (Table 1).

Table 1. Characteristics of the high risk sample (weighted) and the GP-identified sample

	1) High risk sample (N=170)	2) GP-identified sample (N=141)
N (%)		
Mean age (range)	54.6 (19-82)	47.52 (18-83)
Female	124 (74.4%)	100 (70.9%)
Male	43 (25.2%)	41 (29.1%)
Anxiety disorder diagnosis*	67 (39.4%)	113 (80.1%)
Panic disorder	*23 (13.5%)*	*78 (55.3%)*
Generalised anxiety disorder	*23 (13.5%)*	*52 (36.9%)*
Social phobia	*17 (10.1%)*	*29 (20.6%)*
Simple phobia	*11 (6.7%)*	*20 (14.2%)*
Obsessive compulsive disorder	*2 (0.9%)*	*14 (9.9%)*
Post traumatic stress disorder	*1 (0.3%)*	*5 (3.5%)*
Agoraphobia	*19 (11.0%)*	*4 (2.8%)*

*Percentages do not count to 100% because many patients had more than one anxiety disorder

Test results

The results are summarised in Table 2. For the high risk sample the two screening questions of the PHQ showed the best test characteristics, because of an increase in sensitivity. The positive predictive value (PPV) was 76%, the negative predictive value (NPV) was 88% and the overall performance of the PHQ as expressed by the area under the curve was 84% which may be interpreted as moderate to high (Fischer et al. 2003). In GP-identified patients the official algorithm performed best, with a PPV of 96%, a NPV of 38% and the area under the curve was moderate (77%).

Diagnostic value of the PHQ

In the high risk sample, a positive answer on one of the two screening questions of the PHQ significantly increased the odds for a MINI anxiety disorder classification (odds ratio 23.4; 95% confidence interval 6.94 to 78.82). In the GP-identified patients, a positive PHQ (based on the original algorithm) resulted in an odds ratio of 13.89 (95% confidence interval 3.81 to 50.63).

Table 2. Performance of the Patient Health Questionnaire to detect an anxiety disorder in a high risk sample (weighted) and a GP-identified sample

	High risk sample (N=170)								GP-identified sample (N=141)			
	Official algorithm[a]				Screening questions[b]				Official algorithm[a]			
Cross tabulation	a	b	c	d	a	b	c	d	a	b	c	d
	25	8	42	95	49	15	12	93	73	3	40	25
Prevalence	0.39 (67/170)				0.36 (61/170)				0.80 (113/141)			
Positive predictive value	0.77 (25/32) [0.71-0.83]				0.76 (49/64) [0.70-0.83]				0.96 (73/76) [0.93-0.99]			
Negative predictive value	0.69 (95/138) [0.62-0.76]				0.88 (93/105) [0.83-0.93]				0.38 (25/65) [0.30-0.46]			
Positive likelihood ratio	5.1 [4.41-5.79]				5.71 [4.93-6.49]				6.03 [5.12-6.94]			
Negative likelihood ratio	0.68 [0.61-0.75]				0.23 [0.17-0.30]				0.40 [0.32-0.48]			
Sensitivity	0.37 (25/67) [0.30-0.44]				0.80 (49/61) [0.74-0.86]				0.65 (73/113) [0.57-0.72]			
Specificity	0.93 (95/103) [0.89-0.97]				0.86 (93/108) [0.81-0.91]				0.89 (25/28) [0.84-0.94]			
Overall accuracy	0.71 (95+25/170) [0.64-0.78]				0.84 (93+49/170) [0.78-0.89]				0.70 (73+25/141) [0.62-0.77]			
Area under the curve	0.65* [0.64-0.66]				0.83* [0.82-0.84]				0.77 [0.68-0.86]			

a: true positives, b: false positives, c: false negatives, d: true negatives

[a] *Official algorithm panic disorder: All the first four questions are answered with "yes" and four symptoms related to panic attacks are present. Official algorithm general anxiety: The first question is answered with "more than half the days" and three symptoms related to general anxiety are present more than half the days.*

[b] *Screening question for panic disorder ("In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?") is answered with yes AND/OR screening question for general anxiety ("Feeling nervous, anxious, on edge, or worrying a lot about different things") is answered with "more than half the days".*

**Because weighting in the receiver operating characteristics (ROC) analysis is only possible with integer values, the weights were multiplied by 100*

Discussion

Summary of main findings

The results imply that the PHQ may be used as a screener in high risk groups, and to confirm a preliminary anxiety disorder diagnosis made by the GP, but not for ruling out the possibility of a present anxiety disorder in GP-identified patients. In the high risk sample, the performance of the PHQ using the official algorithm was moderate, but the two screening questions of the PHQ showed particularly good test characteristics. A positive score on one of the screening questions significantly increased the odds of receiving an anxiety disorder diagnosis. The PPV was 76%, the NPV was 88% and the area under the curve was moderate to high (83%) in the high risk sample. In the GP-identified sample, a positive score on the official algorithm of the PHQ did adequately predict the presence of an anxiety disorder (PPV of 96%) and significantly increased the odds for receiving an anxiety disorder diagnosis, but the ability of the PHQ to filter out non-cases was inadequate in these patients (NPV of 38%). The are under the curve was moderate (77%) in GP-identified patients.

Strengths and limitations of the study

A strength of this study is its focus on the practical purpose of screening and case-finding. A limitation is that the study was performed within a RCT and not all practices did participate in the screening procedure. The participating practices in this study may thus not be fully representative for the total population of primary care practices. We also may have missed patients who did not want to participate in a randomised controlled trial or who did not want treatment for their anxiety. Nevertheless, in reality probably only patients with a need for treatment will respond to an invitation for a screening procedure, so our findings may be applicable for patients who are in principle motivated for treatment.

Comparison with existing studies

The performance of the PHQ in the high risk sample is consistent with the performance of the panic module in a previous study with a high risk sample consisting of frequent attenders, patients with medically unexplained symptoms and

patients with mental health problems in primary care (Wittkampf *et al.* 2010). The authors also found that using only the screening questions improved the performance of the PHQ substantially and concluded that the PHQ was of moderate value for screening in high risk groups. Other studies have found a better performance of the PHQ (Spitzer *et al.* 1999; Diez-Quevedo *et al.* 2001; Persoons *et al.* 2003). This may be due to the characteristics of our study population (patients at risk for anxiety disorders), with our study design (cross-sectional analysis within a RCT) or with the characteristics of the instrument itself. The Generalised Anxiety Disorder-7 item scale (GAD-7), which is largely similar to the general anxiety module of the PHQ, and was developed by the same research group (Spitzer *et al.* 2006), might be more accurate in detecting an anxiety disorder (Kroenke *et al.* 2007). However, a recent study questioned the ability of the GAD-7 to detect an anxiety disorder other than generalised anxiety disorder (Donker *et al.* 2011). Few studies have examined the characteristics of screening questionnaires in patients identified by their GP. A study using the Hospital Anxiety and Depression Scale (HADS) and the Four Dimensional Symptom Questionnaire (4DSQ) has shown an area under the curve of 76% and 79% respectively (Terluin *et al.* 2009). Although the predictive values found for both the HADS and the 4DSQ in the study of Terluin and colleagues (2009) were more balanced, this may also have been caused by the lower prevalence of mental disorders found in their study (34% versus 80%).

Implications for future research and practice

The high prevalence of anxiety disorders (39%) in the high risk sample suggests that selecting patients from the EMR on the basis of psychological symptoms, social problems or physical symptoms related to anxiety disorders, might be a successful method for selective screening in primary care. This may be especially relevant for patients presenting with physical symptoms because it is more difficult for GPs to recognise anxiety disorders in these patients (Kirmayer *et al.* 1993). The finding that the use of the two screening questions of the PHQ resulted in the best performance is positive, because this makes the screening procedure minimally time consuming. However, when implementing a selective screening procedure, it needs to be followed by a structured approach of further clinical diagnostic procedures and evidence-based

treatment, as recommended in clinical guidelines (National Institute for Health and Clinical Excellence 2011). Therefore, low-intensity interventions need to be available in primary care to be able to treat a large number of patients (Richards & Borglin 2011). Only then selective screening will be an effective way of improving management of anxiety disorders. Considering GPs who referred patients to this study, it is noteworthy that they did correctly suspect the presence of an anxiety disorder in 80% of the cases. This suggests a high specificity of GPs considering anxiety disorders. However, the number of patients that GPs identified varied widely (from 0 to 17). Efforts to improve detection of anxiety disorders may thus be aimed at GPs with a low recognition rate of anxiety disorders. Furthermore, it may be worthwhile to prompt GPs to investigate the presence of an anxiety disorder also in patients with less obvious anxiety symptoms. Subsequently, GPs have the option of using the PHQ to confirm their diagnosis, because a positive PHQ increased the predictive value of the GPs to 96%. We recommend that future diagnostic studies will also pay attention to the practical purposes of screening instruments, to help informing primary care on the best way to use these instruments. Further research will also have to determine whether selective screening will increase the number of patients with anxiety disorders starting with evidence based treatment.

Conclusions

The results of this study show that the two screening questions of the PHQ form a suitable instrument for screening for anxiety disorders in high risk primary care patients. GPs may use the official algorithm of the PHQ as a confirmation of their preliminary diagnosis, however, they are not advised to use the PHQ for ruling out the presence of an anxiety disorder. Following this study, research should focus on the effectiveness of selective screening for anxiety disorders in primary care and on strategies to improve the recognition of anxiety disorders by GPs with a low recognition rate.

REFERENCES

American Psychiatric Association (2001). *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).* American Psychiatric Publishing: Washington, DC.

Andrews, G., Cuijpers, P., Craske, M. G., McEvoy, P. & Titov, N. (2010). Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One* **5**, e13196.

Buszewicz, M. J. & Chew-Graham, C. (2011). Improving the detection and management of anxiety disorders in primary care. *Br J Gen Pract* **61**, 489-490.

Christensen, K. S. & Olesen, F. (2005). Mental health screening may prove effective in primary care. *Br J Gen Pract* **55**, 967.

Diez-Quevedo, C., Rangil, T., Sanchez-Planell, L., Kroenke, K. & Spitzer, R. L. (2001). Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients. *Psychosom.Med* **63**, 679-686.

Donker, T., van Straten, A., Marks, I. & Cuijpers, P. (2011). Quick and easy self-rating of Generalized Anxiety Disorder: validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. *Psychiatry Res* **188**, 58-64.

Dowrick, C., Leydon, G. M., McBride, A., Howe, A., Burgess, H., Clarke, P., Maisey, S. & Kendrick, T. (2009). Patients' and doctors' views on depression severity questionnaires incentivised in UK quality and outcomes framework: qualitative study. *British Medical Journal* **338**, b663.

Eack, S. M., Greeno, C. G. & Lee, B. J. (2006). Limitations of the Patient Health Questionnaire in Identifying Anxiety and Depression in Community Mental Health: Many Cases are Undetected. *Research on Social Work Practice*, 625-631.

Fischer, J. E., Bachmann, L. M. & Jaeschke, R. (2003). A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. *Intensive Care Med* **29**, 1043-1051.

Flensborg-Madsen, T., Tolstrup, J., Sorensen, H. J. & Mortensen, E. L. (2012). Social and psychological predictors of onset of anxiety disorders: results from a large prospective cohort study. *Soc Psychiatry Psychiatr Epidemiol* **47**, 711-721.

Franx, G., Oud, M., De Lange, J., Wensing, M. & Grol, R. (2012). Implementing a stepped care approach in primary care. Results of a qualitative study. *Implement.Sci* **7**, 8.

Gunn, J. M., Palmer, V. J., Dowrick, C. F., Herrman, H. E., Griffiths, F. E., Kokanovic, R., Blashki, G. A., Hegarty, K. L., Johnson, C. L., Potiriadis, M. & May, C. R. (2010). Embedding effective depression care: using theory for primary care organisational and systems change. *Implement.Sci* **5**, 62.

Janssen, E., van de Ven, P., Terluin, B., Verhaak, P., van Marwijk, H., Smolders, M., Van der Meer, K., Penninx, B. & van Hout, H. (2012). Recognition of anxiety disorders by family physicians after rigorous medical record case extraction: Results of the Netherlands Study of Depression and Anxiety. *Gen Hosp Psychiatry*.

Karsten, J., Hartman, C. A., Smit, J. H., Zitman, F. G., Beekman, A. T. F., Cuijpers, P., Does, A. J. W., Ormel, J., Nolen, W. A. & Penninx, B. W. J. H. (2011). Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. *British Journal of Psychiatry* **198**, 206-212.

Kessler, R. C., Ruscio, A. M., Shear, K. & Wittchen, H. U. (2010). Epidemiology of anxiety disorders. *Curr Top Behav Neurosci* **2**, 21-35.

Kessler, D., Bennewith, O., Lewis, G. & Sharp, D. (2002). Detection of depression and anxiety in primary care: follow up study. *Bmj* **325**, 1016-1017.

Kirmayer, L. J., Robbins, J. M., Dworkind, M. & Yaffe, M. J. (1993). Somatization and the recognition of depression and anxiety in primary care. *American Journal of Psychiatry* **150**, 734-741.

Kroenke, K., Spitzer, R. L., Williams, J. B., Linzer, M., Hahn, S. R., deGruy, F. V. & Brody, D. (1994). Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Archives of Family Medicine* **3**, 774-779.

Kroenke, K., Spitzer, R. L., Williams, J. B., Monahan, P. O. & Lowe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann.Intern.Med* **146**, 317-325.

Lowe, B., Grafe, K., Zipfel, S., Spitzer, R. L., Herrmann-Lingen, C., Witte, S. & Herzog, W. (2003). Detecting panic disorder in medical and psychosomatic outpatients: comparative validation of the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire, a screening question, and physicians' diagnosis. *J Psychosom.Res* **55**, 515-519.

National Institute for Health and Clinical Excellence 2009, *Depression in adults: NICE guidance*, National Institue for Health and Clinical Excellence, London.

National Institute for Health and Clinical Excellence 2011, Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. NICE clinical guideline 113.

Ormel, J., Brink, W. v. d., Koeter, M. W., Giel, R., Meer, K. v. d., Willige, G. v. d. & Wilmink, F. W. (1990). Recognition, management and outcome of psychological disorders in primary care: a naturalistic follow-up study. *Psychological Medicine* **20**, 909-923.

Pepe, M. S. (2003). The statistical evaluation of medical tests for classification and prediction., Oxford University Press, New York.

Persoons, P., Luyckx, K., Desloovere, C., Vandenberghe, J. & Fischler, B. (2003). Anxiety and mood disorders in otorhinolaryngology outpatients presenting with dizziness: validation of the self-administered PRIME-MD Patient Health Questionnaire and epidemiology. *Gen Hosp.Psychiatry* **25**, 316-323.

Rasbash, J., Charlton, C., Browne, B. J., Healy, M., & Cameron, B. MLWiN Version 2.1. 2011. University of Bristol, Centre for Multilevel Modelling.

Richards, D. A. (2012). Stepped care: a method to deliver increased access to psychological therapies. *Can J Psychiatry* **57**, 210-215.

Richards, D. A. & Borglin, G. (2011). Implementation of psychological therapies for anxiety and depression in routine practice: two year prospective cohort study. *J Affect Disord* **133**, 51-60.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R. & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J.Clin.Psychiatry* **59 Suppl 20**, 22-33.

Smolders, M., Laurant, M., Verhaak, P., Prins, M., van, M. H., Penninx, B., Wensing, M. & Grol, R. (2009). Adherence to evidence-based guidelines for depression and anxiety disorders is associated with recording of the diagnosis. *Gen Hosp Psychiatry* **31**, 460-469.

Spitzer, R. L., Kroenke, K. & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama* **282**, 1737-1744.

Spitzer, R. L., Kroenke, K., Williams, J. B. & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern.Med* **166**, 1092-1097.

Spitzer, R. L., Williams, J. B., Kroenke, K., Hornyak, R. & McMurray, J. (2000). Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *American Journal of Obstetrics and Gynecology* **183**, 759-769.

SPSS Inc. SPSS 15.0 for Windows. 2006. Chicago.

Terluin, B., Brouwers, E. P., van Marwijk, H. W., Verhaak, P. F. & van der Horst, H. E. (2009). Detecting depressive and anxiety disorders in distressed patients in primary care; comparative diagnostic accuracy of the Four-Dimensional Symptom Questionnaire (4DSQ) and the Hospital Anxiety and Depression Scale (HADS). *BMC.Fam.Pract.* **10**, 58.

Tiemens, B. G., VonKorff, M. & Lin, E. H. B. (1999). Diagnosis of depression by primary care physicians versus a structured diagnostic interview: Understanding discordance. General Hospital Psychiatry **21**, 87-96.

van Vliet, I. M., Leroy, H., & van Megen, H. J. M. (2000). De MINI-Internationaal neuropsychiatrisch interview: een kort gestructureerd diagnostisch interview voor DSM-IV en ICD-10 psychiatrische stoornissen. [The Mini-international Neuropsychiatric Interview: A short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. In Dutch].LUMC: Leiden.

Wittchen, H. U., Kessler, R. C., Beesdo, K., Krause, P., Hofler, M. & Hoyer, J. (2002). Generalized anxiety and depression in primary care: prevalence, recognition, and management. *J Clin Psychiatry* **63 Suppl 8**, 24-34.

Wittkampf, K., Baas, K., van Weert, H., Lucassen, P. & Schene, A. (2010). The psychometric properties of the panic disorder module of the Patient Health Questionnaire (PHQ-PD) in high-risk groups in primary care. *J Affect Disord.*

World Health Organization (1993). The ICD-10 classification of mental health and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization: Geneva.

Chapter 5

Study b

Is the Beck Anxiety Inventory a good tool to assess the severity of anxiety? A primary care study in The Netherlands Study of Depression and Anxiety (NESDA)

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Abstract

Background: Appropriate management of anxiety disorders in primary care requires clinical assessment and monitoring of the severity of the anxiety. This study focuses on the Beck Anxiety Inventory (BAI) as a severity indicator for anxiety in primary care patients with different anxiety disorders (social phobia, panic disorder with or without agoraphobia, agoraphobia or generalised anxiety disorder), depressive disorders or no disorder (controls).

Methods: Participants were 1601 primary care patients participating in the Netherlands Study of Depression and Anxiety (NESDA). Regression analyses were used to compare the mean BAI scores of the different diagnostic groups and to correct for age and gender.

Results: Patients with any anxiety disorder had a significantly higher mean score than the controls. A significantly higher score was found for patients with panic disorder and agoraphobia compared to patients with agoraphobia only or social phobia only. BAI scores in patients with an anxiety disorder with a co-morbid anxiety disorder and in patients with an anxiety disorder with a co-morbid depressive disorder were significantly higher than BAI scores in patients with an anxiety disorder alone or patients with a depressive disorder alone. Depressed and anxious patients did not differ significantly in their mean scores.

Conclusions: The results suggest that the BAI may be used as a severity indicator of anxiety in primary care patients with different anxiety disorders. However, because the instrument seems to reflect the severity of depression as well, it is not a suitable instrument to discriminate between anxiety and depression in a primary care population.

Background

In primary care, many patients present with anxiety symptoms but these are seldom systematically assessed (Bakker *et al.* 2010). To improve anxiety management, assessment of the severity of the anxiety (and subsequent monitoring) is recommended by researchers and also in clinical guidelines (McIntosh *et al.* 2010; Muntingh *et al.* 2009; Roy-Byrne, Wagner, & Schraufnagel, 2005). With regard to depression, the use of severity indicators in primary care is supported by the results of studies showing that patients value the use of questionnaires as a supplement to the diagnosis made by their general practitioner and as evidence that their problems are taken seriously (Dowrick *et al.* 2009). Furthermore, when questionnaires to assess severity are used, higher severity scores are related to better care (i.e. higher prescription rates of antidepressant medication and increased referral to secondary care) (Kendrick *et al.* 2009). Moreover, in some countries incentives are offered when a validated instrument is used at the start of and during the treatment of patients diagnosed with depression (British Medical Association & NHS Employers, 2009). For similar reasons the use of severity scales to assess anxiety symptoms in primary care might be advocated. However, we first have to determine which questionnaires can be used as severity indicators in primary care and what their characteristics are.

As anxiety disorders differ in type and symptoms, assessing the severity of anxiety in general may be more difficult than assessing the severity of depression. General rating scales may not be specific enough to assess the severity of a specific anxiety disorder (i.e. panic disorder or generalised anxiety disorder). However, extensive testing for different forms of anxiety is also not feasible during the short consultations in primary care. Considering its brevity, simplicity, and presumed ability to measure general anxiety, the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988) might be a good candidate for use as a severity indicator. Since its development, the BAI has been widely used in clinical research in mental health care, mainly as a measure of general anxiety (Piotrowski, 1999).

However, the BAI has been disputed for its focus on psychophysiological symptoms linked to panic. The results of several studies have found that patients with panic disorder score higher on the BAI than patients with for example generalised anxiety

disorder (Beck & Steer, 1991; Cox, Cohen, Direnfeld, & Swinson, 1996; Fydrich, Dowdall, & Chambless, 1992; Leyfer, Ruberg, & Woodruff-Borden, 2006). Either way, patients with panic disorder and patients with other anxiety disorders have been found to score significantly higher than patients with no anxiety disorder (Kabacoff, Segal, Hersen, & Van Hasselt, 1997; Steer, Ranieri, Beck, & Clark, 1993; Wetherell & Gatz, 2005). Remarkably, no study has specifically investigated the co-morbidity of anxiety disorders and how this influences BAI scores, even though co-morbidity occurs frequently (De Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002). Furthermore, none of the previous BAI studies have focused on primary care populations.

Another presumed quality of the BAI is its ability to discriminate anxiety from depression (Beck *et al.* 1988). Even though in primary care this might be of less importance than in research settings, it is important to know whether the BAI only measures anxiety or whether it is also sensitive to depressive symptomatology. The results of earlier studies suggest a substantial overlap of the BAI with depressive symptoms, illustrated by a moderate correlation between the BAI and depression scales (Ferguson, 2000). In terms of differences in the BAI scores of anxious and depressed patients, a large difference was found in the original validation study (Beck *et al.* 1988), but in two later studies no difference was found. However, in these studies the authors questioned the results because of limitations in the methodology (Hewitt & Norton, 1993; Steer *et al.* 1993).

In the present study, we investigated whether the BAI reflects the severity of anxiety in primary care patients with different anxiety disorders. The mean scores of several patient groups were compared: healthy controls, patients with one anxiety disorder, patients with multiple anxiety disorders, patients with one depressive disorder, and patients with co-morbid anxiety-depression. The diagnostic groups were separated into patients with no co-morbidity and patients with co-morbidity, to ensure homogeneity of the groups. It was hypothesised that the BAI scores of patients with an anxiety disorder would be higher than the BAI scores of healthy controls or depressed patients. Patients with a panic disorder were expected to score higher than patients in the other anxiety disorder groups. We also expected patients with co-morbid disorders to score higher than patients with no co-morbidity.

Methods

Participants

The participants in this study were recruited for a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA) (Penninx *et al.* 2008). From the baseline sub-sample of 1601 primary care patients in the NESDA cohort we selected all patients with a current anxiety or depressive disorder according to the WHO Composite Interview Diagnostic Instrument (CIDI lifetime version 2.1) and patients with no history of anxiety or depression. DSM-IV classifications of diagnoses within the past month were used to assure present symptomatology. Patients with a history of anxiety or depression, but no current diagnosis, were excluded from the analysis. The mean BAI scores of patients with an anxiety disorder (*N*=276) and patients with a depressive disorder (*N*=155), were compared to the mean BAI scores of a control group of patients with no history of anxiety or depressive disorders (*N*= 513). The NESDA study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre.

Procedures

The primary care sample in the NESDA study was recruited between September 2004 and February 2007 through 65 general practitioners situated in different parts of the Netherlands (Amsterdam, Groningen, and Leiden). A screening questionnaire was sent to 23750 patients between 18 and 65 years of age who had consulted their general practitioner in the past four months. This questionnaire consisted of the Kessler-10 (K-10) (Kessler *et al.* 2002), which screens for affective disorders, supplemented with five questions about anxiety (Extended K-10, or EK-10). The EK-10 showed adequate psychometric properties, with a sensitivity of .90 and a specificity of .75 to detect anxiety or depressive disorders (Donker *et al.* 2010). Participants who returned the EK-10 (*N* =10706, 45.9%), scored positively (*N* = 4592, 43%), gave informed consent (*N*=3420, 74%) and could be contacted (*N*=2995, 88%) had a telephone screening interview based on short-form sections of the CIDI (major depression, dysthymia, social phobia, panic disorder, agoraphobia, and generalised anxiety disorder).

Patients who were unwilling to be interviewed (*N*=267, 9%), were not fluent in Dutch (*N*=86, 3%) or were being treated in a mental health organisation (*N* = 155, 5%), were excluded. All other patients who screened positive on the telephone screening (*N* = 1162, 47%) and a random sample of patients who screened negative (*N* = 924) were contacted for a face-to-face interview. As 437 (24%) participants were unwilling to participate and 39 (2%) could not be contacted or were not fluent in Dutch, 1610 primary care patients were finally included in the NESDA study and completed the baseline assessment. More details about the recruitment process are described elsewhere (Penninx *et al.* 2008). Of the 1610 NESDA participants, 9 patients who did not complete the BAI were excluded from the analysis. The present sample therefore consisted of 1601patients, 617 of whom had at least one current diagnosis of anxiety or depression, 471 had a history of anxiety or depression, and 513 were controls with no history of anxiety or depression.

Assessment

Composite Interview Diagnostic Instrument (CIDI)

The CIDI (version 2.1) is an interview that classifies psychiatric diagnoses according to the DSM-IV (American Psychiatric Association, 2001). It is a widely used interview, which has good interrater reliability (Wittchen *et al.* 1991), high test-retest reliability (Wacker, Battegay, Mullejans, & Schlosser, 2006), and high validity for the classification of depressive and anxiety disorders (Wittchen *et al.* 1989; Wittchen, 1994). CIDI interviews were conducted by specifically trained research assistants. The CIDI classifies diagnoses that were present at some point in the patient's life (lifetime diagnoses), in the past half year and in the past month.

Beck Anxiety Inventory (BAI)

The BAI is a short list describing 21 anxiety symptoms such as "wobbliness in legs", "scared" and "fear of losing control" (Beck *et al.* 1988). Respondents are asked to rate how much each of these symptoms bothered them in the past week, on a scale ranging from 0 (not at all) tot 3 (severely, I could barely stand it). The total score has a minimum of 0 and a maximum of 63. The scale was validated in a sample of 160 psychiatric outpatients with various anxiety and depressive disorders, diagnosed with

the Structured Clinical Interview for DSM-III (Spitzer & Williams, 1983). The BAI has a high internal consistency (Cronbachs *a*= .92) and a test-retest reliability over one week of .75 (Beck *et al.* 1988).

Statistical analysis

All analyses were conducted in SPSS version 15.0 (SPSS Inc., 2006). Regression analysis was performed to examine differences between group scores. The analyses were corrected for age and gender, because age was differentially distributed over the diagnostic groups and because female patients scored significantly higher than male patients in the total sample. All variables were entered simultaneously into the analysis. The analyses were repeated with different groups as the reference group to be able to compare all groups.

Results

Descriptive statistics

The average age of the participants was 45.9 years and the majority of the patients were female (68.8%). Almost one third of the participants had been diagnosed with an anxiety disorder in the past month (*N* = 493, 30.8%). Table 1 shows the age, gender and DSM-IV diagnosis of the participants.

Table 1. Age, gender and current DSM-IV diagnoses of participants (N = 1601)

	N	**%**
All participants	1601	
Age [range]	45.8 [18-65]	
Female gender	1102	68.8%
Any anxiety disorder	**493**	
Age [range]	45.7 [18-65]	
Female gender	346	70.2%
Social phobia*	68	*13.8%*
Panic disorder with agoraphobia*	42	*8.5%*
Panic without agoraphobia*	28	*5.7%*
Agoraphobia*	42	*8.5%*
Generalised anxiety disorder*	34	*6.9%*
>1 anxiety disorder	76	*15.4%*
Co-morbid anxiety & depression	203	*41.2%*
Any depressive disorder	**327**	
Age [Range]	46.2 [18-64]	
Female gender	223	68.2%
Dysthymia*	8	*2.4%*
Major depression*	101	*30.9%*
>1 depressive disorder	15	*4.6%*
Co-morbid depression & anxiety	203	*62.1%*
Patients with a history of anxiety or depression	471	*29.4%*
Controls (no history of anxiety or depression)	513	*32.0%*

*Disorder with no co-morbid anxiety disorder or co-morbid depressive disorder

Many patients with a diagnosis of an anxiety disorder had at least one co-morbid anxiety disorder. The percentage of patients with a co-morbid anxiety disorder varied over the diagnostic groups: anxiety co-morbidity was highest in patients with panic disorder or generalised anxiety disorder (54%) followed by patients with social phobia (51%) and patients with agoraphobia alone (35%). Almost half (41%) of the patients with an anxiety disorder also suffered from a depressive disorder, while 62% of the patients with a depressive disorder were also diagnosed with an anxiety disorder.

Anxiety disorders

Table 2 shows the mean BAI scores of the control group (no history of anxiety or depression), patients with one anxiety disorder and patients with multiple anxiety disorders. Patients with a co-morbid depression were excluded from this analysis (n=203).

Table 2. Mean BAI scores of patients with different anxiety disorders (with no co-morbid depression) and controls

Diagnosis (past month)	N	M	SD
Controls	513	4.09	5.06
Social phobia*	68	12.97	9.03
Panic disorder with agoraphobia*	42	16.00	11.02
Panic disorder without agoraphobia*	28	13.04	6.61
Agoraphobia*	42	11.62	8.51
Generalised anxiety disorder*	34	13.15	5.67
Multiple anxiety disorders	76	18.54	8.54

*Single anxiety disorder diagnosis

Patients with an anxiety disorder scored significantly higher than the controls (p <0.001) and patients with multiple anxiety disorders scored considerably higher than all other groups (p < .05). The mean BAI score of patients with a panic disorder and agoraphobia was significantly higher than the mean score of patients with social phobia (p=0.03) or agoraphobia alone (p<0.001).

Anxiety and depressive disorders

Table 3 shows that the score of depressed patients approximates the score of anxious patients (p = .41). Patients with co-morbid anxiety-depression scored significantly higher than patients with either an anxiety disorder or a depressive disorder alone (p <0.001).

Table 3. Mean BAI scores of patients with a depressive disorder, an anxiety disorder and co-morbid anxiety-depression

Diagnosis (past month)	N	M	SD
Depressive disorder	109	13.34	8.72
Anxiety disorder	214	13.94	8.69
Co-morbid anxiety-depression	203	21.89	10.95

Discussion

The results of our study show that primary care patients with different anxiety disorders score significantly higher than patients with no anxiety or depressive disorder. These results suggest that the BAI does reflect general anxiety in primary care patients. With regard to the different diagnostic groups of anxiety disorders, we did partly confirm the strong focus of the BAI on panic symptoms (Cox *et al.* 1996; Leyfer *et al.* 2006). Patients with a panic disorder and agoraphobia scored significantly higher than patients with agoraphobia alone or social phobia. However, patients with a panic disorder without agoraphobia did not score significantly higher than the other groups. The high scores of patients with a panic disorder and agoraphobia might thus be explained by the severity of this specific disorder. In other studies in which the BAI was used, greater differences were found between the group of patients with a panic disorder and other diagnostic groups (Beck & Steer, 1991; Fydrich *et al.* 1992; Leyfer *et al.* 2006; Steer & Beck, 1996). One reason for this discrepancy in findings might be the setting in which studies took place. Most of the previous studies were conducted in treatment centres for anxiety disorders, while the participants in the present study were actively recruited in primary care, also including patients with previously

undiagnosed anxiety or depression. It is likely that more primary care patients present with less severe forms of panic disorder. Indeed, the mean score of patients with panic disorder in the present study seems to be substantially lower than the scores reported in studies with secondary care patients (Beck & Steer, 1991; Fydrich *et al.* 1992; Leyfer *et al.* 2006; Steer & Beck, 1996) coming closer to the scores of patients with a panic disorder in an epidemiological sample (Hoyer, Becker, Neumer, Soeder, & Margraf, 2002). Furthermore, in the analysis of the present study, patient groups were specifically selected on the basis of (the absence of) co-morbidity, thus resulting in pure diagnostic groups. This may have provided a more accurate estimate of the mean scores of specific patient groups.

Beck and colleagues (Beck *et al.* 1988) claimed that the BAI measures anxiety while minimizing its overlap with depression but this was not sustained by the results of the present study. For practical purposes, this is a two-sided finding. The BAI appears to be robust for depression, but not entirely specific for anxiety in a primary care population. These findings are consistent with the results of earlier studies that compared the total BAI scores of depressed and anxious patients (Hewitt & Norton, 1993; Steer *et al.* 1993). Steer and colleagues relate their findings to the low co-morbidity rate in their sample, but this argument does not hold up in the present study. There could be several explanations why depressed patients score almost as high as anxiety patients. First of all, sub-threshold anxiety experienced by patients with a depressive disorder may have increased their anxiety scores. Sub-threshold anxiety was not assessed in the present study, but previous research has shown that a substantial number of depressed patients also experience some form of (sub-threshold) anxiety (Lowe *et al.* 2008; Roy-Byrne *et al.* 2000). Secondly, somatoform disorders were not classified with the CIDI interview, while these disorders are prevalent in primary care patients with a depressive disorder, and can also cause the physiological symptoms described in the BAI (Mergl *et al.* 2007). A third explanation might be that anxiety and depression share a common underlying factor, often referred to as 'negative affect' (Brown & Barlow, 2009; Lowe *et al.* 2008). There is longstanding debate about this question, growing stronger due to the pressure of the upcoming publication of the DSM-V and fuelled by the considerable prevalence of co-morbidity between anxiety and depression and the symptom overlap on anxiety

and depression scales. With regard to this third hypothesis, the sensitivity of the BAI for shared symptomatology would be more of a quality than a deficiency. Fourthly, total scores for self-report questionnaires, in general, might not be precise enough to measure difficult constructs such as anxiety and depression. There is some evidence that the BAI is able to discriminate between anxiety and depression when items are weighted, as happens in factor analysis (Hewitt & Norton, 1993). However, weighting the items would complicate the use of the BAI to such an extent that its use would not be feasible in primary care.

A strength of this study is the large size of this primary care sample, diagnosed with a valid interview identifying five different anxiety disorders and two depressive disorders. Because of the high prevalence of co-morbidity in patients with anxiety and depressive disorders, such a large sample is needed to compare (sub-)groups of patients with a specific anxiety or depressive disorder. However, even in this large sample, patients with one specific anxiety disorder are scarce, limiting the power of the analyses. Another limitation of the analysis was the skewed distribution of the scores. Although we considered performing a log transformation, we decided to use raw scores to facilitate the interpretability of the scores in clinical practice.

Conclusions

The results indicate that the BAI reflects the severity of anxiety in primary care patients with different anxiety disorders. The use of questionnaires such as the BAI may improve the care that is provided and is desirable from the viewpoint of primary care patients (Dowrick *et al.* 2009). However, as the use of questionnaires in primary care is not common practice, this should be stimulated by means of guidelines, training and education. Further research will be needed to evaluate the usefulness of the BAI in monitoring the severity of anxiety during treatment and over time. In addition, researchers should establish criteria for improvement and remission according to the BAI score, in primary care patients. When questionnaires such as the BAI are used within a framework of care, such as case management or collaborative care, they will optimally help to improve the treatment of primary care patients with anxiety disorders (Gilbody, Sheldon, & Wessely, 2006; Muntingh *et al.* 2009; Roy-Byrne *et al.* 2010).

REFERENCES

American Psychiatric Association 2001, *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV)*, American Psychiatric Publishing, Washington, DC.

Bakker, I. M., van Marwijk, H. W., Terluin, B., Anema, J. R., van, M. W. & Stalman, W. A. (2010). Training GP's to use a minimal intervention for stress-related mental disorders with sick leave (MISS): Effects on performance Results of the MISS project; a cluster-randomised controlled trial. *Patient Education Counseling* **78**, 206-2011.

Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* **56**, 893-897.

Beck, A. T. & Steer, R. A. (1991). Relationship between the Beck Anxiety Inventory and the Hamilton Anxiety Rating Scale with anxious outpatients. *Journal of Anxiety Disorders* **5**, 213-223.

British Medical Association & NHS Employers 2009, Quality and Outcomes framework guidance for GMS contract 2009/10. Delivering investment in general practice. 3rd revision.

Brown, T. A. & Barlow, D. H. (2009). A proposal for a dimensional classification system based on the shared features of the DSM-IV anxiety and mood disorders: implications for assessment and treatment. *Psychological Assessment* **21**, 256-271.

Cox, B. J., Cohen, E., Direnfeld, D. M. & Swinson, R. P. (1996). Does the Beck Anxiety Inventory measure anything beyond panic attack symptoms? *Behaviour Research and Therapy* **34 (11-12)**, 949-954.

De Graaf, R., Bijl, R. V., Smit, F., Vollebergh, W. A. & Spijker, J. (2002). Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *American Journal of Psychiatry* **159**, 620-629.

Donker, T., Comijs, H., Cuijpers, P., Terluin, B., Nolen, W., Zitman, F. & Penninx, B. (2010). The validity of the Dutch K10 and extended K10 screening scales for depressive and anxiety disorders. *Psychiatry Research*.

Dowrick, C., Leydon, G. M., McBride, A., Howe, A., Burgess, H., Clarke, P., Maisey, S. & Kendrick, T. (2009). Patients' and doctors' views on depression severity questionnaires incentivised in UK quality and outcomes framework: qualitative study. *British Medical Journal* **338**, b663.

Ferguson, R. J. (2000). Using the Beck Anxiety Inventory in Primary Care. In *Handbook of psychological assessments in primary care settings* (ed. M. E. Maruish). Lawrence Erlbaum: Mahwah, NJ.

Fydrich, T., Dowdall, D. & Chambless, D. L. (1992). Reliability and validity of the Beck Anxiety Inventory. *Journal of Anxiety Disorders* **6**, 55-61.

Gilbody, S., Sheldon, T. & Wessely, S. (2006). Should we screen for depression? *British Medical Journal* **332**, 1027-1030.

Hewitt, P. L. & Norton, G. R. (1993). The Beck Anxiety Inventory: A psychometric analysis. *Psychological Assessment* **5**, 408-412.

Hoyer, J., Becker, E. S., Neumer, S., Soeder, U. & Margraf, J. (2002). Screening for anxiety in an epidemiological sample: predictive accuracy of questionnaires. *Journal of Anxiety Disorders* **16**, 113-134.

Kabacoff, R. I., Segal, D. L., Hersen, M. & Van Hasselt, V. B. (1997). Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. *Journal of Anxiety Disorders* **11**, 33-47.

Kendrick, T., Dowrick, C., McBride, A., Howe, A., Clarke, P., Maisey, S., Moore, M. & Smith, P. W. (2009). Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. *British Medical Journal* **338**, b750.

Kessler, R. C., Andrews, G., Colpe, L. J., Hiripi, E., Mroczek, D. K., Normand, S. L., Walters, E. E. & Zaslavsky, A. M. (2002). Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological Medicine* **32**, 959-976.

Leyfer, O. T., Ruberg, J. L. & Woodruff-Borden, J. (2006). Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders. *Journal of Anxiety Disorders* **20**, 444-458.

Lowe, B., Spitzer, R. L., Williams, J. B., Mussell, M., Schellberg, D. & Kroenke, K. (2008). Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. *General Hospital Psychiatry* **30**, 191-199.

McIntosh, A., Cohen, A., Turnbull, N., Esmonde, L., Dennis, P., Eatock, J., Feetam, C., Hague, J., Hughes, I., Kelly, J., Kosky, N., Lear, G., Owens, L., Ratcliffe, J., & Salkovskis, P. (2010). *Clinical guidelines and evidence review for panic disorder and generalised anxiety disorder*, University of Sheffield/London: National Collaborating Centre for Primary Care, Sheffield.

Mergl, R., Seidscheck, I., Allgaier, A. K., Moller, H. J., Hegerl, U. & Henkel, V. (2007). Depressive, anxiety, and somatoform disorders in primary care: prevalence and recognition. *Depression and Anxiety* **24**, 185-195.

Muntingh, A. D. T., van der Feltz-Cornelis CM, Van Marwijk, H. W. J., Spinhoven, P., Assendelft, W. J. J., de Waal, M. W., Hakkaart-van, R. L., Ader, H. J. & Van Balkom, A. J. L. M. (2009). Collaborative stepped care for anxiety disorders in primary care: aims and design of a randomized controlled trial. *BMC Health Services Research* **9**, 159.

Penninx, B. W., Beekman, A. T., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P., Cuijpers, P., de Jong, P. J., van Marwijk, H. W., Assendelft, W. J., van der, M. K., Verhaak, P., Wensing, M., de Graaf, R., Hoogendijk, W. J., Ormel, J. & van Dyck, R. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research* **17**, 121-140.

Piotrowski, C. (1999). The status of the Beck Anxiety Inventory in contemporary research. *Psychological Reports* **85**, 261-262.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.

Roy-Byrne, P. P., Stang, P., Wittchen, H. U., Ustun, B., Walters, E. E. & Kessler, R. C. (2000). Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. *British Journal of Psychiatry* **176**, 229-235.

Roy-Byrne, P. P., Wagner, A. W. & Schraufnagel, T. J. (2005). Understanding and treating panic disorder in the primary care setting. *Journal of Clinical Psychiatry* **66 Suppl 4**, 16-22.

Spitzer, R. L. & Williams, J. B. W. (1983). *Instruction manual for the Structured Clinical Interview for the DSM-III (SCID)*. New York State Psychiatric Institute, Biometrics Research Department: New York.

SPSS Inc. SPSS 15.0 for Windows. 2006. Chicago.

Steer, R. A. & Beck, A. T. (1996). Generalized anxiety and panic disorders: Response to Cox, Cohen, Direnfeld, and Swinson (1996). *Behaviour Research and Therapy* **34**, 955-957.

Steer, R. A., Ranieri, W. F., Beck, A. T. & Clark, D. A. (1993). Further evidence for the validity of the Beck Anxiety Inventory with psychiatric outpatients. *Journal of Anxiety Disorders*, 195-205.

Wacker, H. R., Battegay, R., Mullejans, R., & Schlosser, C. (2006). Using the CIDI-C in the general population. In *Psychiatry: A world perspective* (eds. C. N. Stefanis, A. D. Rabavilas and C. R. Soldatos). Elsevier Science Publishers: Amsterdam.

Wetherell, J. L. & Gatz, M. (2005). The Beck Anxiety Inventory in Older Adults With Generalized Anxiety Disorder. *Journal of Psychopathology and Behavioral Assessment* **27**, 17-24.

Wittchen, H. U. (1994). Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research* **28**, 57-84.

Wittchen, H. U., Burke, J. D., Semler, G., Pfister, H., Von, C. M. & Zaudig, M. (1989). Recall and dating of psychiatric symptoms. Test-retest reliability of time-related symptom questions in a standardized psychiatric interview. *Archives of General Psychiatry* **46**, 437-443.

Wittchen, H. U., Robins, L. N., Cottler, L. B., Sartorius, N., Burke, J. D. & Regier, D. (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *British Journal of Psychiatry* **159**, 645-53, 658.

Chapter 6

General discussion

Background and objectives of this thesis

Anxiety disorders are chronically intermittent conditions that are highly prevalent, disabling and costly. Patients with anxiety disorders may be adequately treated in primary care using a chronic and integrated care perspective. However, there are many barriers in primary care for providing continuous, evidence based care for anxiety disorders. These barriers consider patient, provider and health care system characteristics. A collaborative stepped care model may be an effective and efficient method to improve the quality of primary care for patients with anxiety disorders, by introducing mental health expertise into primary care, ensuring evidence-based treatment, systematic monitoring and follow-up and supporting self-management of the patient within a framework of collaboration between professionals. Panic disorder and generalised anxiety disorder are target conditions for collaborative stepped care, because they are often inadequately treated in primary care while evidence based treatments suitable for primary care do exist. In this thesis, the effectiveness of collaborative stepped care for panic disorder and generalised anxiety disorder in primary care was evaluated. Furthermore, the costs of collaborative stepped care relative to its effectiveness and manners to improve recognition and assessment of anxiety disorders were examined.

Summary of the main findings

In **chapter 2** it was investigated whether collaborative care for adult patients with anxiety disorders was more effective than usual primary care. A systematic search of the literature identified five randomised controlled trials that met the inclusion criteria. Four studies originated from the United States and one from Germany. The studies included a total of 1931 participants and were of varying methodological quality. The included studies provide evidence that collaborative care may be effective for anxiety disorders in general and is significantly more effective than care as usual for patients with panic disorder. More studies are needed that evaluate the effectiveness of collaborative care for anxiety disorders other than panic disorder and that are conducted in other countries than the United States.

In **chapter 3** we described a cluster randomised controlled trial to compare collaborative stepped care to usual primary care for patients with panic disorder or

generalised anxiety disorder. The trial was carried out in 43 primary care practices and a total of 180 patients with panic disorder or generalised anxiety disorder were enrolled. Patients in the collaborative care stepped group (N=114) received guided self-help as a first step, followed by CBT and antidepressants when necessary. Care was provided by a care manager and the general practitioner (GP), who both had access to the advice of a psychiatrist. Patients in the care as usual group (N=66) received care as usual through their GP. Data were collected by means of patient-completed questionnaires at baseline, at 3, 6, 9 and 12 months. The primary outcome measure was the Beck Anxiety Inventory (BAI). Collaborative stepped care was more effective than usual primary care in reducing anxiety symptoms at all time points, with the largest difference at 12 months (diff. -6.84, 95% confidence interval -10.13 to -3.55). The clinical effect of collaborative stepped care compared to care as usual was small to moderate.

Alongside the cluster randomised controlled trial we conducted a cost-effectiveness analysis (**chapter 4**). The difference in quality of life gained and health care and productivity costs generated in the collaborative stepped care group and care as usual group was compared. Collaborative stepped care led to a marginal increase in health care costs of €351, but the incremental gains in quality of life (diff. 0.05 QALY) outweighed these extra costs. The extra health care costs in the collaborative stepped care group were mostly due to contacts with the care manager. Including productivity costs in the analysis strengthened the results, as productivity costs were higher in the care as usual group. Consequently, collaborative stepped care was more effective and less costly compared to care as usual, which makes it a highly cost-effective intervention.

In **chapter 5** we assessed the added value of the Patient Health Questionnaire (PHQ) in the detection and diagnosis of anxiety disorders in two patient groups: 1) patients at high risk for (developing) anxiety disorders, 2) patients identified by their GP as possibly having an anxiety disorder. In patients at high risk for developing anxiety disorders, the use of only two screening questions of the PHQ showed the best characteristics. The positive predictive value was 76% and the negative predictive value was 88% in the high risk patients. In patients identified by the GP as possibly having an anxiety disorder, the full PHQ did adequately predict the presence of an

anxiety disorder (positive predictive value of 96%), but the ability of the PHQ to filter out non-cases (negative predictive value of 38%) was inadequate in these patients. These results imply that the PHQ may be used as a screener in high-risk groups, and to confirm a preliminary diagnosis of the GP, but not for ruling out the possibility of a present anxiety disorder in GP-identified patients. Furthermore, we examined the ability of the Beck Anxiety Inventory (BAI) to reflect the severity of the anxiety in patients with different anxiety disorders. Primary care patients with an anxiety disorder (N=493) had a significantly higher score (Mean (M)=13.9, standard deviation (SD)=8.7) than patients without a disorder (N=513; M=4.1; SD=5.1). Patients with co-morbid anxiety and depression (N=203; M=21.9, SD=11) scored significantly higher than patients with a single disorder, albeit an anxiety disorder (N=214; M= 13.9; SD=8.7) or a depressive disorder (N=109; M=13.3; SD=8.7). Of the anxiety disorders, patients with panic disorder and agoraphobia had the highest mean score (M=16, SD=11).We concluded that the BAI may be used as a severity indicator for anxiety disorders in primary care.

Interpretation of the results and comparison with existing literature

Effectiveness of collaborative stepped care compared to care as usual

Our hypothesis that collaborative stepped care would lead to improved patients outcomes compared to care as usual was confirmed. At all time points, patients in the collaborative stepped care group showed a significantly larger reduction in anxiety symptoms. Because of the complexity of the collaborative stepped care intervention it is difficult to say what elements of the intervention contributed most to the larger decrease in anxiety symptoms as observed in the collaborative stepped care group. The guided self-help method may have induced cognitive and behavioural change in intervention patients (van Boeijen *et al.* 2005). Most patients and professionals appreciated the guided self-help method as a practical and effective method (Bouman *et al.* 2010). The structured method of working with scheduled appointments, a treatment protocol and standardised evaluation of symptoms was certainly different from the usual working methods of the mental health professionals. The provision of evidence based psychological treatment was probably lower in the care as usual group. Unfortunately, we were unable to extract the type of intervention patients received in

the care as usual group. However, if we look at the 50% of the care as usual patients who received counselling with or without antidepressant medication from their GP, it appears that only 40% of those received regular consultations (defined as ≥ 4 contacts in 15 weeks). Furthermore, based on previous surveys with primary care professionals in the Netherlands, we may assume that the provision of structured evidence based interventions was minimal (Zwaanswijk & Verhaak 2009; Sinnema *et al.* 2010). The fact that the care managers had a mental health background and received supervision from experienced psychotherapists may have further improved the quality of treatment of the collaborative stepped care intervention, because these aspects of the collaborative care model have been identified as crucial for its effectiveness in the literature (Bower *et al.* 2006). Another element of collaborative stepped care that may be responsible for a larger effectiveness was that patients who needed a more intensive or different form of treatment were identified and provided medication (11%) or a smooth transition to a different health care professional (14%). In the introduction it was suggested that collaborative stepped care might lead to the avoidance of unnecessary prescription of medication or referral to secondary care. Our data show that fewer patients in the collaborative care group used antidepressants during the follow-up period (31% versus 45%), while collaborative stepped care was more effective. No difference appeared between collaborative stepped care and care as usual in the number of contacts patients had in specialty mental health care. However, it is difficult to define which of these contacts were "unnecessary". The finding that the decrease in symptoms in the collaborative stepped care group was sustained until twelve months is particularly important. A relapse of symptoms is often seen in patients with anxiety disorders and was also visible in the scores of patients in the care as usual group. This sustained decrease of symptoms in the collaborative stepped care group may have been the result of the relapse prevention that was offered to 60% of the patients that successfully concluded treatment. In conclusion, the results of our study confirm that usual primary care can be improved by implementing evidence based mental health in primary care, with support from mental health professionals and structural monitoring and follow-up (i.e. collaborative stepped care).

Discrepancy between the continuous and dichotomous outcomes in the RCT

In contrast to the significant differences found on the continuous outcome measure of the Beck Anxiety Inventory (BAI), we did not find a difference in the time to response (≥ 50% reduction in BAI score) or remission (BAI ≤ 11) between patients in the collaborative stepped care and care as usual group. This discrepancy between the two outcome measures may partly be attributed to the lower power of the dichotomous analysis to detect a difference (Streiner 2002). Another (more important) explanation for the discrepancy between the continuous and dichotomous outcome measure lies in the distribution of BAI scores. It appeared that in 40% of the patients in the care as usual group the BAI score remained stable or even increased from baseline to 12 month follow-up, while in the collaborative stepped care group this happened in only 20% of the patients (Figure 1). Furthermore, a larger proportion of the collaborative stepped care patients showed a large decrease (>1 standard deviation) in symptoms. While these differences are visible on the continuous measure, they are less apparent in the dichotomous outcomes.

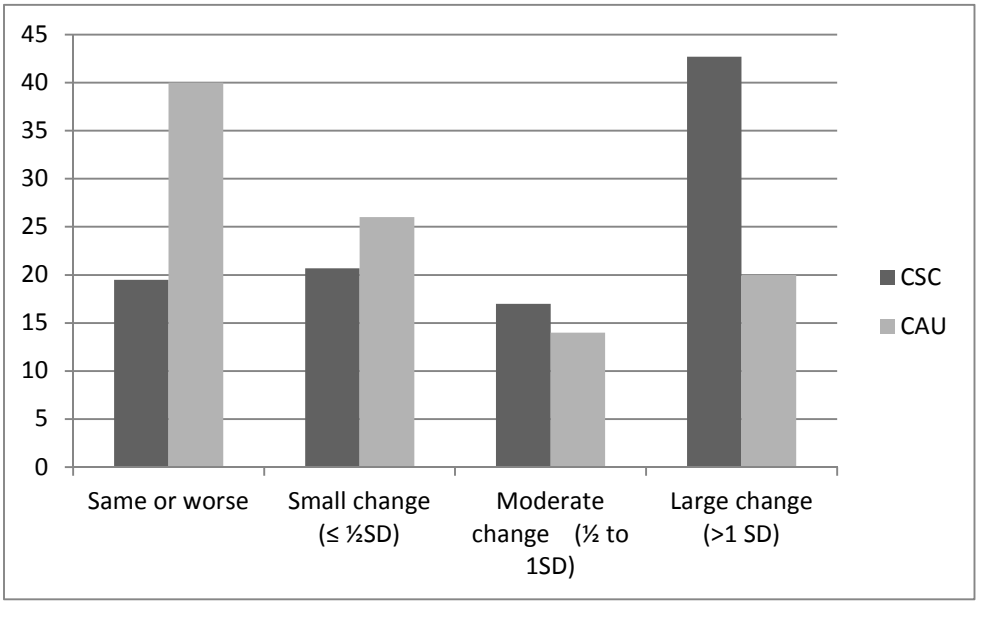


Figure 1. Distribution of change scores in the collaborative stepped care group and the care as usual group

Comparison of the RCT with other collaborative care studies

The results of our study are comparable to the results found in collaborative care studies conducted in the United States (see chapter 2). However, with the exception of the study of Rollman and colleagues (Rollman *et al.* 2005), we found smaller effect sizes during the first nine months of follow-up than found in the North American studies. This may be related to the difference in the intensity of the interventions used. The collaborative care intervention of the two latest trials of Roy-Byrne and colleagues (Roy-Byrne *et al.* 2005; Roy-Byrne *et al.* 2010) started with an intensive intervention, in most cases consisting of a combination of CBT and antidepressant medication. Conversely, we used a stepped care intervention, with an advice to GPs to prescribe medication only if the patient did not sufficiently respond to the first two CBT-based steps. Hence, the smaller effect size in the early stages of our study may be an effect of the stepped care method we used, with patients responding at different stages in treatment. Compared to a German trial on collaborative care for anxiety disorders (Konig *et al.* 2009), our intervention was more effective. As suggested in chapter 2, this is probably due to an inadequate implementation of the intervention in the study of König and colleagues. The similarity in effect of our collaborative stepped care intervention compared to collaborative care interventions in the United States may be an indication for the external validity of the model for different health care settings. In depression research, it was already shown that collaborative care leads to quality improvement in different health care settings (Thota *et al.* 2012). However, more research is needed to draw conclusions on the relative effectiveness of collaborative (stepped) care for anxiety disorders in different health care settings.

Comparison of the RCT with similar studies from the Netherlands

Van Boeijen and colleagues (2005) developed the guided self-help method that was used in our study. They compared the guided-self-help method to guideline based usual care and cognitive behavioural therapy by an experienced therapists in a primary care population in a RCT. Surprisingly, they found no differential effects between the three groups (van Boeijen *et al.* 2005). The guided self-help method alone was as effective as usual primary care, while in our study the guided self-help method, as part of a collaborative stepped care approach, was more effective than usual primary care.

Although the studies may not be directly comparable, we may speculate about explanations for these differences. The care as usual provided in the study of van Boeijen and colleagues (2005) was highly effective, while the guided self-help method seemed to be less effective in reducing anxiety symptoms than the collaborative stepped care intervention evaluated in our study. The authors explain the high effectiveness of care as usual in their study by the high number of patients that received antidepressants or were referred to specialty mental health care. Furthermore, the number of patients included by the GPs in the care as usual condition in the study of Van Boeijen and colleagues was small (26 patients) and may not be representative for care as usual. The higher effectiveness of the collaborative stepped care intervention compared to the guided self-help method could be related to the additional elements in the collaborative stepped care intervention, such as monitoring of symptoms, a second or third step if patients did not respond to treatment, active follow-up of patients, and the involvement of a care manager and psychiatrist.

Seekles and colleagues (2011) did compare a stepped care program for patients with anxiety or depressive disorders to usual primary care. The stepped care program comprised three subsequent steps, consisting of guided self-help, problem solving treatment and pharmacological treatment or referral to specialty mental health care. A care manager (psychiatric nurse) coordinated care and provided problem solving treatment. Almost all (92%) of the 120 included patients had a diagnosis of an anxiety disorder. Their intervention did not lead to a greater effectiveness than care as usual. The authors explain this insignificant finding by difficulties in implementing the stepped care program and the relatively mild, but chronic symptoms of depression and anxiety in their screened population (Seekles *et al.* 2011). A complicating factor in the design of the intervention of Seekles and colleagues (2011) may be that the care manager did not guide the self-help method. Guidance through email or telephone was available from a junior psychologist, but only if the patient requested this which may have resulted in a low adherence to the program.

Huijbregts and colleagues (2012) evaluated the effectiveness of a collaborative care intervention compared to usual primary care for patients with a major depression in a cluster randomised trial. Their collaborative care program consisted of a choice of problem solving treatment and/or antidepressant medication, with care coordination

and monitoring by a care manager and access to specialist input of a consultant psychiatrist with IT support. They recruited patients through a screening procedure and through referral by the GP (referrals were only made by GPs in the collaborative care group). They found that collaborative care led to a significantly higher response rate than care as usual in the short term and also in the long term for patients referred by their GP. However, it is difficult to compare these results because both the interventions and the population (depression or anxiety) differed between the two studies.

Cost-effectiveness of collaborative stepped care for anxiety disorders

To our knowledge, this was the first study that assessed the cost-effectiveness of collaborative stepped care for anxiety disorders (chapter 4). As we expected, collaborative stepped care was cost-effective compared to care as usual. Health care costs were, however, higher in the collaborative stepped care group compared to care as usual. The higher costs of €351,- per patient were largely caused by the extra contacts with the care manager (€177). The premise of stepped care to induce a more efficient use of resources was thus not supported by the results of our study. However, because the costs of care as measured in our RCT were not particularly high the question is whether further decreasing contacts with health care professionals can be realised while sustaining the positive effects of the intervention. Furthermore, the productivity costs caused by sickness absence were higher in the care as usual group. Including the productivity costs in the cost-effectiveness analysis resulted in a higher effectiveness and lower costs of the collaborative care intervention, which means that taking a societal perspective, collaborative stepped care was dominant compared to care as usual.

The added value of questionnaires in detecting anxiety disorders

As already laid out in this thesis, the recognition, diagnosis and assessment of anxiety disorders is a condition for the provision of collaborative stepped care treatment. Therefore, we assessed the added value of two questionnaires in the diagnostic process (chapter 5). The PHQ seems to be a valuable instrument for screening high-risk populations. However, screening for anxiety disorders in high risk populations

will not necessarily improve patient outcomes. For example, Baas and colleagues found that the use of the PHQ as a depression screener in primary care did not substantially increase the number of patients starting with treatment for depression (Baas *et al.* 2009): only 1% of the patients who were sent a screening questionnaire eventually started treatment. It appeared that many patients who were screened did not accept the diagnosis of depression or did not have a need for treatment (Wittkampf *et al.* 2008). In our study, 3% of the patients who were sent a screening questionnaire participated in the RCT, which may mean that screening for anxiety disorders is not much more effective than for depression. In conclusion, the effectiveness of screening high risk populations for anxiety disorders is not yet clear and further research is necessary to examine whether selective screening will lead to improved management of anxiety disorders.

How to improve the recognition and diagnosis of anxiety disorders?

The PHQ had a limited added value for improving detection of anxiety disorders in patients identified by their GP as having a probable anxiety disorder. However, that does not mean that questionnaires are useless in the diagnostic process. Patients do appreciate the use of questionnaires which they perceive as a thorough examination of their symptoms. Moreover, GPs who use a screening instrument feel that it helps them explain the diagnosis to patients (Dowrick *et al.* 2009). If GPs are trained and adequately supported in working with screening instruments, this may eventually lead to better recognition and diagnosis of anxiety disorders. Sinnema and colleagues may shed light on this issue, as they are currently conducting a study using tailored advice to GPs to improve recognition, diagnosis and treatment of depressive and anxiety disorders (Sinnema *et al.* 2011).

Assessing the severity of anxiety with a questionnaire

Measuring the severity of anxiety is an important part of the treatment of anxiety disorders. The severity of anxiety may be used as an indication for stepped care treatment: a low severity of anxiety may be treated by a low intensity treatment, while a high severity of anxiety may be an indication for a more intensive form of treatment (Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ 2010). The

BAI seems to give an adequate indication of the severity of anxiety in different anxiety disorders (chapter 5). Besides the ability to measure the severity of anxiety across anxiety disorders, the BAI has the advantage that it is a short and easy to use instrument, which makes it easily applicable in clinical practice.

Methodological considerations

Collaborative care was provided in a naturalistic setting

A strength of the cluster RCT (chapter 3) was that we were able to conduct a pragmatic trial in a naturalistic setting. Few RCTs considering collaborative care have used existing staff in providing collaborative care (Craven & Bland 2006). All professionals that participated in our study (GPs, care managers and psychiatrist) were recruited in practice settings and underwent additional training to provide collaborative stepped care. This enabled us to estimate the effects of collaborative stepped care as implemented in daily practice. Because we used cluster randomisation, we could also correctly estimate care as usual. The GPs in the care as usual group had access to all the options normally available to them to deliver mental health care, such as prescribing medication, providing counselling themselves or referring the patient to a mental health professional. The GPs in the care as usual group also had access to a one of the 15 mental health professionals who were allocated to the care as usual group. However, only 12.5% of the care as usual patients were referred to these professionals. To indicate that care as usual in our study reflects care as usual in daily practice, we may compare our data to data from a large naturalistic cohort study conducted in primary care (NESDA). The cohort of primary care patients with an anxiety disorder in this study showed the same reduction in anxiety symptoms (measured with the BAI) over the course of one year as seen in our care as usual group (van Beljouw *et al.* 2010).

Additional strengths

Another strength is that we designed a comprehensive collaborative stepped care program, with evidence based interventions suitable for primary care, a valid monitoring instrument and a treatment plan to increase adherence and foster collaboration between the care manager and the GP. We provided training for all

professionals and supervision for care managers. We included sufficient patients to detect a significant difference between collaborative stepped care and care as usual. The additional cost-effectiveness analysis conducted alongside the RCT is also a strength, because information about cost-effectiveness is essential for decision making. Furthermore, as few stepped care trials have included a cost-analysis, this study provides insight into the cost-effectiveness of stepped care.

External validity

Patients were recruited for this study in various primary care practices in the western part of the Netherlands, located in urban areas as well as rural areas. The anxiety disorders in our sample were fairly chronic, with a mean age of onset of 31, while the mean age of participants was 46. Our study included a relatively large proportion of patients with a basic (45%) to intermediate level (35%) of education, which is important because these patients often do not receive adequate treatment (Prins *et al.* 2010). Furthermore, many patients had a comorbid chronic medical condition (73%) or a comorbid depression (30%) which are prevalent comorbid conditions in anxiety disorders (Roy-Byrne *et al.* 2008; Penninx *et al.* 2011). This suggests that collaborative stepped care is effective for a heterogeneous group of patients with panic disorder and/or generalised anxiety disorder. The primary care practices that participated in our study may differ from the average primary care practice in the Netherlands. Participating GPs may have had a special interest in anxiety disorders. However, this applies to both GPs in the collaborative stepped care group as well as the care as usual group. Furthermore, as the collaborative stepped care treatment was standardised to a substantial degree we may assume that other mental health care professionals and GPs are able to achieve similar effects in treatment.

The pitfalls of cluster randomisation

We have experienced that collaborative stepped care is a complex intervention, which makes it difficult to test in a randomised controlled trial (Richards 2012). The choice to use cluster randomisation was based on the notion that there is a risk of contamination in patient randomised trials using complex interventions such as collaborative care (Richards *et al.* 2008). However, cluster randomisation suffers from

a number of limitations that became apparent during our study. The first problem we encountered was the imbalance between the number of patients referred to the study by GPs in the collaborative stepped care group and the care as usual group. GPs in the collaborative stepped care group referred 137 patients to the study, while GPs in the care as usual group referred 70 patients. We tried to stimulate GPs to refer patients, by regular reminders through newsletters, telephone calls or e-mails, but it was very difficult to increase the number of referrals from GPs in the care as usual group. Perhaps GPs in the care as usual group were less motivated to refer patients to the study, because they did not see an advantage for themselves or their patients in participating. Another possibility is that GPs in the collaborative stepped care group had an increased attention for the study because they were confronted with the new method in the treatment of their patients. A second problem of cluster randomisation is that it carries a risk of selection bias: GPs in the collaborative stepped care group may refer a different type of patients than GPs in the control group. To diminish the risk of selection bias, all patients were interviewed with the MINI PLUS by a blinded interviewer and patients were kept blinded for the condition of their GP until baseline. This meant that patients had to be willing to accept both treatment as usual and collaborative stepped care. Despite of these efforts, differences between the collaborative stepped care group and the care as usual group at baseline appeared. Patients in the collaborative stepped care group had a higher severity of anxiety and did less often take antidepressants at baseline. The difference in antidepressant use may be explained by an early effect of the intervention, as we instructed GPs in the collaborative stepped care group not to prescribe antidepressants to patients they referred to the study. We do not have a valid explanation for the higher severity of anxiety in patients in the collaborative stepped care group. In the analyses we corrected for possible errors introduced by selection bias with propensity scores and we corrected for anxiety severity at baseline. Antidepressant use at baseline did not have a significant influence on treatment effect. Furthermore, we conducted a sensitivity analysis on the effect of the intervention in patients that were selected from the electronic medical record (and were thus not subject to selection bias of the GP) and this analysis yielded similar results. Nonetheless, it is better to prevent than to cure. A strategy to prevent selection bias in a cluster RCT is to exclusively use a

screening procedure carried out by blinded research assistants. A drawback of this approach is that it stands further away from common practice as patients usually are not identified using a screening procedure. Another option would be to use patient randomisation instead of cluster randomisation. Notwithstanding the risk of contamination, it may be preferable to eliminate the risk of selection bias and give a conservative estimate of the effects of collaborative stepped care compared to care as usual. As research has shown that behavioural change in GPs is hard to establish (Lin *et al.* 1997) and a system change is needed to induce improved patient outcomes (Gilbody *et al.* 2003), the risk of contamination of the effect may be acceptable.

Suboptimal implementation of the collaborative stepped care intervention

Another limitation of our trial is that, despite extensive supervision and instruction of the care managers and GPs, the stepped care model was not followed through as intended in a substantive amount of cases (see Figure 2). A significant proportion of patients did either not complete step 1 or did not continue to step 2 while remission was not yet achieved. Some of these patients were referred to another mental health professional, but others discontinued mental health treatment in general. The patients who did not complete step 1 had different reasons for discontinuing the program: they had other problems they needed to focus on (legal issues or problems in their family), they were dissatisfied with treatment or they experienced no anxiety symptoms anymore. An exploratory analysis revealed that the patients who did not complete step 1 were more often widowed or divorced, were selected from the electronic medical record instead of selected by their GP, had a lower level of education, were more often taking antidepressants at baseline, were older and suffered from more chronic conditions. Further research should evaluate the predictive value of these characteristics on treatment outcome and the effects of extra efforts to increase adherence of these patients to collaborative stepped care.

Most patients who did not want to continue with step 2 were already satisfied with their achievements and did not desire further treatment. The relatively low rate (10%) of patients continuing to the second step compares to the results of a recent stepped care trial (Seekles *et al.* 2011) and an analysis of the implementation of stepped care in routine practice (Richards *et al.* 2012). Apparently, 90% of the patients recovers after a

minimal intervention, is referred to another health care professional, or desires no further treatment. The question is whether this is a limitation of the stepped care approach. One could argue that stepped care is not necessary if only 10% makes use of a subsequent step. Patients could simply be referred after step one to another mental health care professional or continue treatment with medication. However, the second step in our protocol was reasonably effective. Furthermore, the possibility of continuity of care may seem more attractive to patients than being referred to yet another professional.

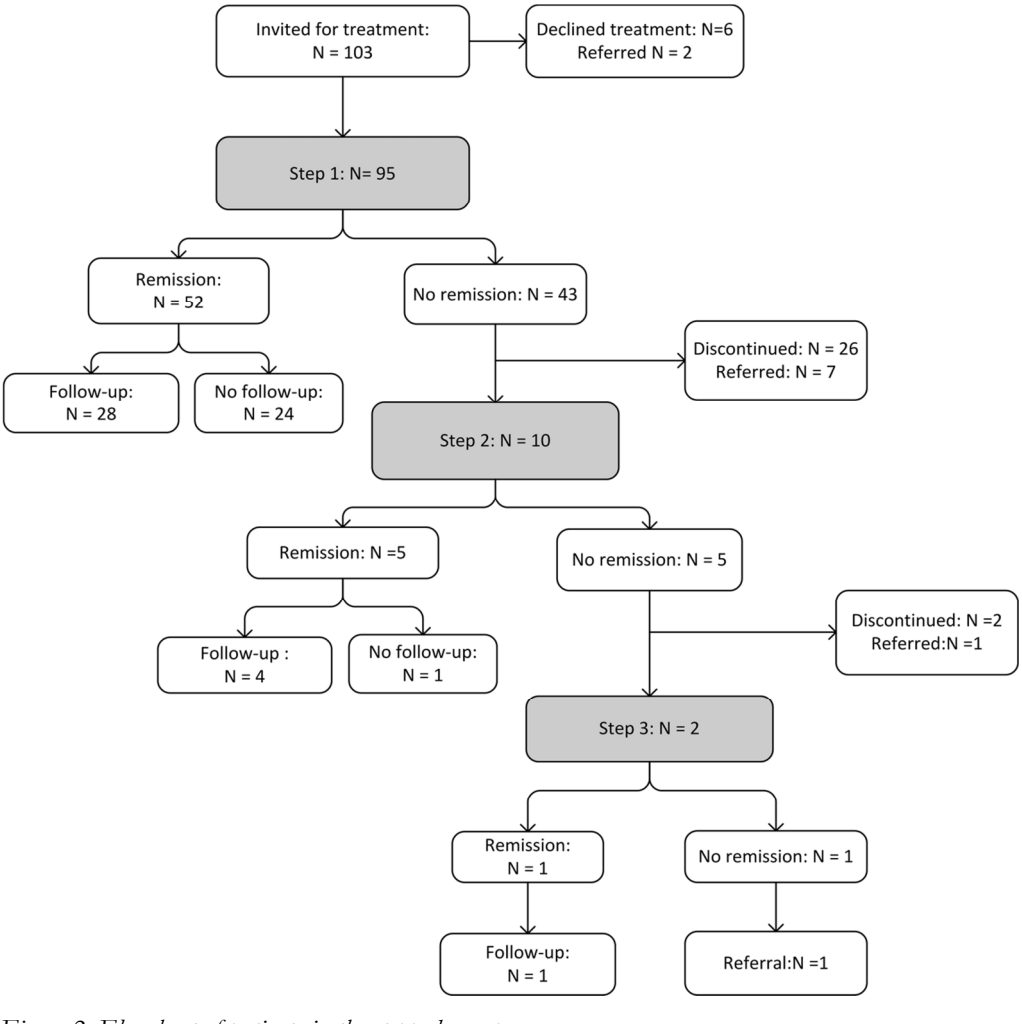


Figure 2. Flowchart of patients in the stepped care program

Choosing criteria for remission

Another issue is whether we chose the right criteria for remission. We determined the criteria for remission based on the BAI scores of the NESDA cohort. Using the criteria for reliable change (Jacobson & Truax 1991b) we calculated the mean between the population with the disorder (patients with a panic disorder or generalised anxiety disorder) and the healthy population (patients without an anxiety disorder). This resulted in a score of 11 on the BAI. We added to this criterion the requirement of a 50% reduction in score for patients who scored below 22 at baseline. In our analyses however, we only kept the criterion of a score of 11 or below to avoid overlap between response and remission and it is likely that the care managers placed more emphasis on this criterion as well. On the one hand, it is possible that our criteria were too strict, as many patients decided to terminate treatment while they did not meet our criteria for remission yet. On the other hand, as (subclinical) anxiety symptoms are an important predictor of a relapse of the anxiety disorder (Batelaan *et al.* 2010), it is of arguable importance to treat the anxiety disorder until a low level of symptoms has been reached. These arguments, together with the agreement between our cut-off score and the norm scores based on a population sample (Ferguson 2000), support the validity of our criterion. Furthermore, because the use of the BAI to determine remission is a fairly simple method and because both care managers and patients appreciated the monitoring of symptoms with the BAI (Bouman *et al.* 2010; van Weelden *et al.* 2010), we conclude that our remission criterion is practical and sufficiently valid.

Improving the collaborative stepped care intervention

Three aspects of the collaborative stepped care intervention deserve special attention as they leave room for improvement: patient adherence, psychiatrist involvement and training and supervision of the care managers. Patient adherence may be increased by offering patients a choice between different forms of low-intensity treatments (Kwan *et al.* 2010). Furthermore, early evaluation of the treatment plan may prevent dissatisfied patients from discontinuing the program. However, as noted earlier, personal circumstances probably also prevented patients from engaging in the collaborative stepped care program and this kind of problems may not be averted.

The involvement of the psychiatrists in our study was lower than seen in other collaborative care trials. The care managers and GPs stated that they solved most of the problems amongst themselves and rarely felt the need for the specialist advice of a psychiatrist (Bouwmeester *et al.* 2010; Bouman *et al.* 2010). Furthermore, the supervision of the care managers by a cognitive behavioural therapist instead of the psychiatrist may have hindered the involvement of the psychiatrist with treatment. Moreover, in contrast to other collaborative care studies, we used psychiatrists working in practice as consulting psychiatrist. The psychiatrists may have been less active in approaching the care managers or GPs themselves, because the collaborative stepped care study was just a small part of their activities (Ouwerkerk 2010). Psychiatrists also thought that their role was to give their expert opinion only when there were difficulties in treatment and did not think it was their job (or that it was necessary) to monitor the total caseload of the care managers. A web-based tracking system, such as used in some collaborative care studies (Roy-Byrne *et al.* 2010; Huijbregts *et al.* 2012) might enhance contact between the primary care professionals and the psychiatrist. Such a system could also be used as an evaluation tool, with a shared patient record including charts of symptom scores.

For care managers without any experience with CBT, the training of two days in CBT was short and they had limited confidence in their CBT skills. Conversely, care managers who had previously received training in CBT were confident in providing CBT because they had easy access to the advice of the supervising cognitive behavioural therapists. Extra training for care managers in CBT may thus improve quality of treatment. Furthermore, although our intention was that care managers attended supervision sessions once every three weeks, this was not feasible in practice. It appeared to be difficult to organise supervision sessions for the care managers, as they had a small caseload (one to fifteen patients each over the course of the study period) and had to attend the supervision sessions outside their working hours. Nonetheless, the care managers valued the supervision sessions as informative and important for the quality of their work (Bouman *et al.* 2010). Supervision attendance could be increased by offering supervision during working hours and at the office of the care manager. Individual supervision sessions by telephone and larger caseloads for care managers may also improve the frequency of supervision sessions.

Focus on two anxiety disorders

We chose to include only patients with panic disorder or generalised anxiety disorder, as both disorders are prevalent, disabling and costly, and because there are short-duration treatments available for both disorders (van Boeijen *et al.* 2005; Seekles *et al.* 2012). Therefore, our results are limited to patients with panic disorder and generalised anxiety disorder. To maximise the utility of collaborative stepped care, it would be better to include social phobia as well, because this disorder is also prevalent and disabling (Barrera & Norton 2009) and may also be adequately treated with cognitive behavioural therapy in a collaborative care framework (Roy-Byrne *et al.* 2010). However, as only one RCT of a short-duration psychological treatment of social phobia in primary care has been identified (Seekles *et al.* 2012), this kind of intervention needs to be studied more thoroughly before incorporating this anxiety disorder into a collaborative stepped care program.

Limited information about effectiveness for subgroups and mediating variables

In this thesis, limited attention was paid to the effectiveness for subgroups of patients. It may be interesting to look at differential effects for patients with different types of comorbidities, level of education or other demographic or clinical variables. Furthermore, information about mediating variables such as coping style may provide interesting insights into the working mechanisms of the interventions. Ideally, we could create a prognostic model of patient flow through the stepped care program resulting in prognostic factors for adherence, response and remission.

Implications for practice

Implementing collaborative stepped care

Much effort is needed to implement a complex intervention such as collaborative stepped care in primary care which requires different levels of involvement. Especially the organisational changes that are necessary for collaborative stepped care, including the involvement of a psychiatrist and the supervision of care managers are a challenge for current Dutch primary care. Training of professionals and guidance in implementing the new approach will be necessary, as research has shown that it is extremely difficult to change the habits of busy primary care personnel (Grol *et al.*

2005). This is also confirmed by the findings from our study that simply placing a mental health professional in primary care does not automatically lead to a frequent use of this professional for anxiety treatment.

Fortunately, examples of implementation efforts for collaborative (stepped) care are available from other countries. One example is the DIAMOND project (Depression Improvement Across Minnesota, Offering a New Direction) in Minnesota in the United States (Lauren Crain *et al.* 2012). In this statewide project an independent quality improvement organisation supports a collaborative effort of health care payers and health care professionals to implement collaborative care for depression management in primary care. They provide training and certification, tailored implementation support and an online tracking system. Almost 100 medical groups and clinics joined the DIAMOND project and researchers aim to evaluate data of more than 2000 patients. Another promising initiative is the Increasing Access to Psychological Therapies (IAPT) program in the United Kingdom (Richards & Borglin 2011). The goal of the program is to increase access to psychological therapies using a collaborative stepped care approach as a framework to provide care. The IAPT program is an initiative from the government that provides services similar to those in the DIAMOND project, with a focus on depression and other common mental health problems. Two demonstration sites tested the implementation of guidelines and it appeared that the site that used a stepped care approach with short-duration therapies was able to treat 3 to 4 times more patients than the site that followed a more traditional approach of delivering psychological therapies. Outcome data of the program were very promising (Richards & Borglin 2011). These two projects show that implementing collaborative stepped care is feasible, however, not without a considerable effort from the government or health care payers.

Required policies

An important step towards effective implementation of collaborative stepped care for anxiety disorders is the revision of the Dutch guideline for general practitioners, that now advises a stepped care approach for anxiety disorders (Hassink-Franke *et al.* 2012). However, to facilitate implementation of collaborative stepped care in the Netherlands further, several adjustments in the Dutch health care system are required.

First of all, the financial resources that are available for the placement of a psychiatric nurse, social worker or a psychologist in the primary care practice to support the GP in mental health tasks ("praktijkondersteuner huisarts GGZ" (POH-GGZ), from now on referred to as psychiatric nurse) are very important for the implementation of collaborative care, because this professional may function as a care manager. In 2011 psychiatric nurses were employed in an estimated 35% of all primary care practices in the Netherlands (Landelijke Vereniging Georganiseerde eerste lijn 2011). It is important that there are no restrictions placed by health care insurers on the number of sessions the psychiatric nurse is allowed to provide. Furthermore, the psychiatric nurse needs to be able to attend supervision sessions. In addition, the financial fees that patients are obliged to pay for consulting a primary care psychologist or a psychiatrist as was commissioned in 2012 need to be abolished, since patients who do not sufficiently respond to the collaborative stepped care treatment need to have access to the services of those professionals.
In 2011 the Dutch Health Care Authority (Nederlandse Zorgautoriteit) has written an advisory report about reforming primary mental health care (Nederlandse Zorgautoriteit 2011). Their advice to expand the function of the psychiatric nurse in primary care is a positive development for the implementation of collaborative stepped care. Furthermore, the reimbursement of primary care consultations by psychiatrists as proposed by the Dutch Health Care Authority would facilitate the implementation of psychiatric consultation in collaborative care.

Implementing the use of questionnaires in clinical practice

The use of questionnaires in primary mental health care is not common practice. This may be caused by the equivocal findings about the additive value of questionnaires for the recognition of mental disorders, or by the idea that the existing questionnaires are not suitable for primary care (Van Rijswijk *et al.* 2009). The Four Dimensional Symptom Questionnaire was developed specifically for use in primary care practice (Terluin *et al.* 2006) and has been successfully implemented in an estimated third of the Dutch primary care practices (Sinnema *et al.* 2010). An advantage of the 4DSQ is that it measures anxiety, depression, distress and somatisation, which are four prevalent and frequently comorbid conditions in primary care. However, the 4DSQ

might not be very accurate in detecting generalised anxiety disorder (Terluin *et al.* 2009) and the ability of the 4DSQ to measure the severity and fluctuations of anxiety has yet to be studied. To increase the use of questionnaires in primary care, there are several requirements that must be met. First, it must be clear for primary care personnel which instrument they should use considering a specific disorder and if it may be used for screening or measuring severity (or both). Preferably, there should be a limited amount of short and simple questionnaires for the most prevalent disorders. Clinical guidelines could be used to advice professionals on which instruments to use, where to find them and how to use them. Second, primary care professionals must know what the advantages are of using the instrument. Therefore more research is needed to assess the practical use of questionnaires i.e. for screening in high risk groups, assisting in diagnosis or for monitoring symptoms in primary care patients. A different stimulating factor for GPs may be to incorporate the use of questionnaires in a quality certificate of the Dutch college of GPs (Nederlands Huisartsen Genootschap). The internet may play a role in increasing the accessibility of questionnaires (Donker *et al.* 2011). Lastly, it should be clear that a questionnaire cannot replace but only complement the clinical judgement of the GP or another health care professional. This is important both for addressing the concerns of GPs that questionnaires may replace their clinical judgement (Dowrick *et al.* 2009) and for ensuring the quality of the diagnostic process. The option to financially reward GPs for the use of questionnaires, does not seem to be desirable (Dowrick *et al.* 2009).

Transforming primary mental health care

Collaborative stepped care as described in this thesis is just one treatment method for one class of disorders. In reality, the GP has to cope with many different kinds of symptoms, disorders and patients. The diagnosis of mental disorders may be particularly difficult because symptoms vary in intensity and are often accompanied by other symptoms or problems. Furthermore, patients' demands for help are frequently not related to their anxiety problems. Therefore, the GP needs adequate skills and resources to recognise, diagnose and treat the patient. It was already suggested that a form of standardisation of the diagnosis such as the routine use of the 4DSQ or PHQ may help. Furthermore, the GP can be assisted by a psychiatric nurse or psychologist

to investigate the nature of the symptoms (with the aid of a questionnaire), the demand for help of the patient and the different possibilities for assistance or treatment. Ideally, the primary care team formulates a treatment plan according to the severity and duration of the symptoms, the preferences of the patient and the available resources. To realise this, the primary care team would need a mental health care 'toolkit' with preventive interventions for patients with only symptoms, collaborative stepped care for those with a disorder and local resources for referral for patients with a severe disorder or predominantly social or relational problems. For patients with recurrent episodes, diagnosis of a psychologist or psychiatrist may be required together with an adequate follow-up on the treatments received, as many patients might fall through the cracks of the primary care system. However, such a systematic approach to mental health problems in primary care does not yet exist. Pilot projects will be necessary to examine the need for and feasibility of such an approach and to design pathways for integrated primary mental health care.

Implications for further research

Research on care models for comorbidity or multimorbidity

It was already stated that the collaborative stepped care intervention needs to be expanded to anxiety disorders other than panic disorder and generalised anxiety disorder. Furthermore, more research is needed about integrated care for patients with multiple chronic conditions. As stressed in the introduction, the presence of multiple chronic conditions, or multimorbidity, is increasingly prevalent in our aging populations (van Oostrom *et al.* 2011). However, for many chronic conditions clinical guidelines exist and in our current health care system it is impossible for GPs to adhere to all of these guidelines (Ostbye *et al.* 2005). Consequently, there is an urgent need to integrate care for different conditions (Vrijhoef 2010). The chronic care model may be used as a framework to reorganise care and to create individualised health care plans in which different aspects of health care are described and which are regularly updated (Boyd *et al.* 2010). A care manager may coordinate care for the patients, keep contact with the different health care providers involved and make decisions together with the patient about goals in treatment. A patient may choose to focus on one chronic condition or goal, for instance the anxiety disorder, and actively

work on the chosen health problem. For example, Katon and colleagues (2012) designed a collaborative care intervention for patients with depression and coronary heart disease and/or diabetes mellitus (Katon *et al.* 2012). In their intervention, the patient was assisted by a nurse care manager, who was supervised by different specialists and also provided problem solving treatment. Although the intervention was not effective in improving the medical parameters important for coronary heart disease or diabetes, depression symptoms significantly improved. Similar studies are warranted to provide guidelines on how to organise health care for patients with comorbidity or multimorbidity.

Other relevant topics

Other relevant topics for further research have emerged from the discussion of our findings. Risk factors for non-response as well as factors that increase the benefits of collaborative stepped care need to be identified to improve its effectiveness. Further research is also warranted to identify effective strategies to improve recognition and increase the number of patients receiving evidence based treatment for anxiety disorders. Research aimed at decreasing health care costs is also needed, for example by identifying target groups for costs savings. Lasts, research aimed at finding opportunities to integrate care for multiple chronic conditions and to define standards for integrated primary mental health care is desirable.

Conclusion

In the introduction it was suggested that collaborative stepped care may be the solution to several important problems in primary care: infrequent initiation of treatment with evidence based psychological therapies, a low intensity of collaboration between health care professionals and the absence of structural monitoring and follow-up. Collaborative stepped care did lead to an increased quality of care in all of these issues and to improved patient outcomes. However, collaborative stepped care is not *the* solution to all problems encountered in primary care for anxiety disorders. As stated above, the effectiveness of collaborative stepped care leaves room for improvement and more research is needed about the cost-effectiveness of collaborative stepped care for patients with different anxiety disorders and to integrate

care for patients with comorbid conditions. Furthermore, although questionnaires may help, diagnosing an anxiety disorder in primary care remains complex. However, we may conclude that collaborative stepped care is a valuable intervention that improves the quality of primary care for anxiety disorders. Although further research is warranted, implementation of collaborative stepped care in daily practice is justified as the intervention is highly cost-effective. Substantial efforts are needed to transform primary care for anxiety disorders.

REFERENCES

Baas, K. D., Wittkampf, K. A., van Weert, H. C., Lucassen, P., Huyser, J., van den Hoogen, H., van de Lisdonk, E., Bindels, P. E., Bockting, C. L., Ruhe, H. G. & Schene, A. H. (2009). Screening for depression in high-risk groups: prospective cohort study in general practice. *Br J Psychiatry* **194**, 399-403.

Barrera, T. L. & Norton, P. J. (2009). Quality of life impairment in generalized anxiety disorder, social phobia, and panic disorder. *J Anxiety Disord* **23**, 1086-1090.

Batelaan, N. M., de Graaf, R., Penninx, B. W. J. H., Van Balkom, A. J. L. M., Vollebergh, W. A. M. & Beekman, A. T. F. (2010). The 2-year prognosis of panic episodes in the general population. *Journal of Affective Disorders* **121**.

Bouman, T., Muntingh, A. D., & Van der Feltz-Cornelis, C. M. (2010) Care Managers' Evaluation of the Implementation of a Collaborative Care Model for the Treatment of Anxiety Disorders. Unpublished manuscript.

Bouwmeester, T. R., Muntingh, A. D., & Van der Feltz-Cornelis, C. M. (2010). General practitioners' evaluation of the implementation of a collaborative stepped care model for the treatment of anxiety disorders. Unpublished manuscript.

Bower, P., Gilbody, S., Richards, D., Fletcher, J. & Sutton, A. (2006). Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. *British Journal of Psychiatry* **189**, 484-493.

Boyd, C. M., Reider, L., Frey, K., Scharfstein, D., Leff, B., Wolff, J., Groves, C., Karm, L., Wegener, S., Marsteller, J. & Boult, C. (2010). The effects of guided care on the perceived quality of health care for multi-morbid older persons: 18-month outcomes from a cluster-randomized controlled trial. *J Gen Intern Med* **25**, 235-242.

Craven, M. A. & Bland, R. (2006). Better practices in collaborative mental health care: an analysis of the evidence base. *Can J Psychiatry* **51**, 7S-72S.

Donker, T., van Straten, A., Marks, I. & Cuijpers, P. (2011). Quick and easy self-rating of Generalized Anxiety Disorder: validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. *Psychiatry Res* **188**, 58-64.

Dowrick, C., Leydon, G. M., McBride, A., Howe, A., Burgess, H., Clarke, P., Maisey, S. & Kendrick, T. (2009). Patients' and doctors' views on depression severity questionnaires incentivised in UK quality and outcomes framework: qualitative study. *British Medical Journal* **338**, b663.

Ferguson, R. J. (2000). Using the Beck Anxiety Inventory in Primary Care. In *Handbook of psychological assessments in primary care settings* (ed. M. E. Maruish). Lawrence Erlbaum: Mahwah, NJ.

Gilbody, S., Whitty, P., Grimshaw, J. & Thomas, R. (2003). Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *Jama* **289**, 3145-3151.

Grol, R., Wensing, M., & Eccles, M. (2005). Improving patient care. The implementation of change in clinical practice., Elsevier.

Hassink-Franke, L. J. A., Terluin, B., Van heest, F. B., Hekman, J., Van Marwijk, H. W. J. & Van Avendonk, M. J. P. (2012). NHG-standaard Angst (tweede herziening). [The NHG

guideline anixety. Second revision of the NHG guideline Anxiety disorders.]. *Huisarts & Wetenschap*, 68-77.

Huijbregts, K. M., de Jong, F. J., Van Marwijk, H. W. J., Beekman, A. T. F., Adèr, H., Hakkaart-Van Roijen, L., Unutzer, J. & Van der Feltz-Cornelis C.M. (2012). A target-driven Collaborative Care model for Major Depressive Disorder is effective in primary care in the Netherlands. A Randomized Clinical Trial from the Depression Initiative. *Journal of Affective Disorders,* accepted for publication.

Jacobson, N. S. & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* **59**, 12-19.

Katon, W., Russo, J., Lin, E. H. B., Schmittdiel, J., Ciechanowski, P., Ludman, E., Peterson, D., Young, B. & Von Korff, M. (2012). Cost-effectiveness of a multicondition collaborative care intervention: a randomized controlled trial. *Arch Gen Psychiatry* **69**, 506-514.

Konig, H. H., Born, A., Heider, D., Matschinger, H., Heinrich, S., Riedel-Heller, S. G., Surall, D., Angermeyer, M. C. & Roick, C. (2009). Cost-effectiveness of a primary care model for anxiety disorders. *Br J Psychiatry* **195**, 308-317.

Kwan, B. M., Dimidjian, S. & Rizvi, S. L. (2010). Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behav Res Ther* **48**, 799-804.

Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ 2010, Multidisciplinaire Richtlijn Angststoornissen (tweede revisie). [Multidisciplinary guideline for anxiety disorders (second revision). In Dutch].

Landelijke Vereniging Georganiseerde eerste lijn. Poh-ggz Nieuwsbrief [Newsletter. In Dutch]. 2011.

Lauren Crain, A., Solberg, L. I., Unutzer, J., Ohnsorg, K. A., Maciosek, M. V., Whitebird, R. R., Beck, A. & Molitor, B. A. (2012). Designing and Implementing Research on a Statewide Quality Improvement Initiative: The DIAMOND Study and Initiative. *Med Care.*

Lin, E. H., Katon, W. J., Simon, G. E., Von Korff, M., Bush, T. M., Rutter, C. M., Saunders, K. W. & walker, E. A. (1997). Achieving guidelines for the treatment of depression in primary care: is physician education enough? *Med Care* **35**, 831-842.

Nederlandse Zorgautoriteit (2011). *Advies Basis GGZ.*

Ostbye, T., Yarnall, K. S. H., Krause, K. M., Pollak, K. I., Gradison, M. & Michener, J. L. (2005). Is there time for management of patients with chronic diseases in primary care? *Ann Fam Med* **3**, 209-214.

Ouwerkerk, M., Muntingh, A.D.T. & Van der Feltz-Cornelis, C.M. (2010) Moving collaborative stepped care from a trial to the real world. Evaluation by mental health professionals. Unpublished manuscript.

Penninx, B. W., Nolen, W. A., Lamers, F., Zitman, F. G., Smit, J. H., Spinhoven, P., Cuijpers, P., de Jong, P. J., van Marwijk, H. W., der Meer, K. V., Verhaak, P., Laurant, M. G., de, G. R., Hoogendijk, W. J., der Wee, N. V., Ormel, J., van, D. R. & Beekman, A. T. (2011). Two-year course of depressive and anxiety disorders: Results from the Netherlands Study of Depression and Anxiety (NESDA). *J.Affect.Disord.*

Prins, M. A., Verhaak, P. F., Smolders, M., Laurant, M. G., Van der Meer, K., Spreeuwenberg, P., van Marwijk, H. W., Penninx, B. W. & Bensing, J. M. (2010). Patient

Factors Associated with Guideline-concordant Treatment of Anxiety and Depression in Primary Care. *J Gen Intern Med.*

Richards, D. A. (2012). Stepped care: a method to deliver increased access to psychological therapies. *Can J Psychiatry* **57**, 210-215.

Richards, D. A. & Borglin, G. (2011). Implementation of psychological therapies for anxiety and depression in routine practice: two year prospective cohort study. *J Affect Disord* **133**, 51-60.

Richards, D. A., Bower, P., Pagel, C., Weaver, A., Utley, M., Cape, J., Pilling, S., Lovell, K., Gilbody, S., Leibowitz, J., Owens, L., Paxton, R., Hennessy, S., Simpson, A., Gallivan, S., Tomson, D. & Vasilakis, C. (2012). Delivering stepped care: an analysis of implementation in routine practice. *Implement.Sci* **7**, 3.

Richards, D. A., Lovell, K., Gilbody, S., Gask, L., Torgerson, D., Barkham, M., Bland, M., Bower, P., Lankshear, A. J., Simpson, A., Fletcher, J., Escott, D., Hennessy, S. & Richardson, R. (2008). Collaborative care for depression in UK primary care: a randomized controlled trial. *Psychological Medicine* **38**, 279-287.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.

Roy-Byrne, P. P., Davidson, K. W., Kessler, R. C., Asmundson, G. J., Goodwin, R. D., Kubzansky, L., Lydiard, R. B., Massie, M. J., Katon, W., Laden, S. K. & Stein, M. B. (2008). Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* **30**, 208-225.

Seekles, W., Cuijpers, P., Kok, R., Beekman, A., van, M. H. & van, S. A. (2012). Psychological treatment of anxiety in primary care: a meta-analysis. *Psychol Med*, 1-11.

Seekles, W., van Straten, A., Beekman, A., van Marwijk, H. & Cuijpers, P. (2011). Stepped care treatment for depression and anxiety in primary care. a randomized controlled trial. *Trials* **12**, 171.

Sinnema, H., Franx, G., Spijker, J., Ruiter, M., Van Haastrecht, H., Verhaak, P. F. M., & Nuijen, J. (2010). Geboden zorg bij depressie en richtlijn-aanbevelingen: aanknopingspunten voor het bevorderen van implementatie van richtlijnen. In *Trendrapportage GGZ 2010. Deel 3: Kwaliteit en effectiviteit.* (ed. J. Nuijen). Trimbos Instituut: Utrecht.

Sinnema, H., Franx, G., Volker, D., Majo, C., Terluin, B., Wensing, M. & van, B. A. (2011). Randomised controlled trial of tailored interventions to improve the management of anxiety and depressive disorders in primary care. *Implement.Sci* **6**, 75.

Streiner, D. L. (2002). Breaking up is hard to do: the heartbreak of dichotomizing continuous data. *Can J Psychiatry* **47**, 262-266.

Terluin, B., van Marwijk, H. W., Ader, H. J., de Vet, H. C., Penninx, B. W., Hermens, M. L., van Boeijen, C. A., van Balkom, A. J., van der Klink, J. J. & Stalman, W. A. (2006). The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. *BMC.Psychiatry* **6**, 34.

Terluin, B., Brouwers, E. P. M., van Marwijk, H. W. J., Verhaak, P. F. M. & Van der Horst, H. E. (2009). Detecting depressive and anxiety disorders in distressed patients in primary care; comparative diagnostic accuracy of the Four-Dimensional Symptom Questionnaire (4DSQ) and the Hospital Anxiety and Depression Scale (HADS). *BMC Fam Pract* **10**, 58.

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease, D. E., Jr. & Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med* **42**, 525-538.

van Beljouw, I. M., Verhaak, P. F., Cuijpers, P., van Marwijk, H. W. & Penninx, B. W. (2010). The course of untreated anxiety and depression, and determinants of poor one-year outcome: a one-year cohort study. *BMC Psychiatry* **10**, 86.

van Boeijen, C. A., van Oppen, P., van Balkom, A. J., Visser, S., Kempe, P. T., Blankenstein, N. & van Dyck, R. (2005). Treatment of anxiety disorders in primary care practice: a randomised controlled trial. *Br J Gen Pract.* **55**, 763-769.

van Oostrom, S. H., Picavet, H. S., van Gelder, B. M., Lemmens, L. C., Hoeymans, N., Verheij, R. A., Schellevis, F. G. & Baan, C. A. (2011). [Multimorbidity and comorbidity in the Dutch population--data from general practices]. *Ned.Tijdschr.Geneeskd.* **155**, A3193.

Van Rijswijk, E., van Hout, H., van de Lisdonk, E., Zitman, F. & Van Weel C. (2009). Barriers in recognising, diagnosing and managing depressive and anxiety disorders as experienced by Family Physicians; a focus group study. *BMC Fam Pract* **10**, 52.

van Weelden, O., Muntingh, A. D. T., & Van der Feltz-Cornelis, C. M. (2010). Shedding new light on the treatment of anxiety disorders. A qualitative study exploring patient experiences with the collaborative stepped care method., Unpublished manuscript.

Vrijhoef, H. J. M. (2010). The future is to chronically ill [Chronisch zieken hebben de toekomst. Inaugurele rede. In Dutch].

Wittkampf, K. A., van Zwieten, M., Smits, F. T., Schene, A. H., Huyser, J. & van Weert, H. C. (2008). Patients' view on screening for depression in general practice. *Fam Pract* **25**, 438-444.

Zwaanswijk, M. & Verhaak, P. F. M. (2009). Effectieve kortdurende interventies voor psychische problemen. Kennissynthese over hun toepasbaarheid in de huisartsenvoorziening. [Effective, short duration interventions for psychological problems. Review of their applicability in Dutch primary care. In Dutch], NIVEL, Utrecht.

Addendum

Summary

Background and objectives of this thesis

Anxiety disorders are chronically intermittent conditions that are highly prevalent, disabling and costly. Patients with anxiety disorders may be adequately treated in primary care using a chronic and integrated care perspective. However, there are many barriers in primary care for providing continuous, evidence based care for anxiety disorders. These barriers consider patient, provider and health care system characteristics. A collaborative stepped care model may be an effective and efficient method to improve the quality of primary care for patients with anxiety disorders, by introducing mental health expertise into primary care, ensuring evidence-based treatment, systematic monitoring and follow-up and supporting self-management of the patient within a framework of collaboration between professionals. Panic disorder and generalised anxiety disorder are target conditions for collaborative stepped care, because they are often inadequately treated in primary care while evidence based treatments suitable for primary care do exist. In this thesis, the effectiveness of collaborative stepped care for panic disorder and generalised anxiety disorder in primary care was evaluated. Furthermore, the costs of collaborative stepped care relative to its effectiveness and manners to improve recognition and assessment of anxiety disorders were examined.

The effectiveness of collaborative care for anxiety disorders in primary care

In **chapter 2** it was investigated whether collaborative care for adult patients with anxiety disorders was more effective than usual primary care. A systematic search of the literature identified five randomised controlled trials that met the inclusion criteria. Four studies originated from the United States and one from Germany. The studies included a total of 1931 participants and were of varying methodological quality. The included studies provide evidence that collaborative care may be effective for anxiety disorders in general and is significantly more effective than care as usual for patients with panic disorder. More studies are needed that evaluate the effectiveness of collaborative care for anxiety disorders other than panic disorder and that are conducted in other countries than the United States.

The effectiveness of collaborative stepped care for panic disorder and generalised anxiety disorder

In **chapter 3** we described a cluster randomised controlled trial to compare collaborative stepped care to usual primary care for patients with panic disorder or generalised anxiety disorder. The trial was carried out in 43 primary care practices and a total of 180 patients with panic disorder or generalised anxiety disorder were enrolled. Patients in the collaborative stepped care group (N=114) received guided self-help as a first step, followed by cognitive behavioural therapy (CBT) and antidepressants when necessary. Care was provided by a care manager and the general practitioner (GP), who both had access to the advice of a psychiatrist. Patients in the care as usual group (N=66) received care as usual through their GP. Data were collected by means of patient-completed questionnaires at baseline, at 3, 6, 9 and 12 months. The primary outcome measure was the Beck Anxiety Inventory (BAI). Collaborative stepped care was more effective than usual primary care in reducing anxiety symptoms at all time points, with the largest difference at 12 months (diff. -6.84, 95% confidence interval -10.13 to -3.55). The clinical effect of collaborative stepped care compared to care as usual was small to moderate.

The cost-utility of collaborative stepped care for panic disorder and generalised anxiety disorder

Alongside the cluster randomised controlled trial we conducted a cost-utility analysis. The difference in quality of life gained and health care and productivity costs generated in the collaborative stepped care group and care as usual group was compared. Collaborative stepped care led to a marginal increase in health care costs of €351, but the incremental gains in quality of life (diff. 0.05 QALY) outweighed these extra costs. The extra health care costs in the collaborative stepped care group were mostly due to contacts with the care manager. Including productivity costs in the analysis strengthened the results, as productivity costs were higher in the care as usual group. Consequently, collaborative stepped care was more effective and less costly compared to care as usual, which makes it a highly cost-effective intervention (**chapter 4**).

The additive value of questionnaires for screening and assisting in the diagnostic process

In **chapter 5** we assessed the added value of the Patient Health Questionnaire (PHQ) in the detection and diagnosis of anxiety disorders in two patient groups: 1) patients at high risk for (developing) anxiety disorders, 2) patients identified by their GP as possibly having an anxiety disorder. In patients at high risk for developing anxiety disorders, the use of only two screening questions of the PHQ showed the best characteristics. The positive predictive value was 76% and the negative predictive value was 88% in these high risk patients. In patients identified by the GP as possibly having an anxiety disorder, the full PHQ did adequately predict the presence of an anxiety disorder (positive predictive value of 96%), but the ability of the PHQ to filter out non-cases (negative predictive value of 38%) was inadequate in these patients. These results imply that the PHQ may be used as a screener in high-risk groups, and to confirm a preliminary diagnosis of the GP, but not for ruling out the possibility of a present anxiety disorder in GP-identified patients. In the second part of **chapter 5**, we examined the ability of the Beck Anxiety Inventory (BAI) to reflect the severity of the anxiety in a large cohort of primary patients (NEDSA cohort) with various anxiety disorders, depressive disorders and healthy controls. Primary care patients with an anxiety disorder (N=493) had a significantly higher score (Mean (M)=13.9, standard deviation (SD)=8.7) than patients without a disorder (N=513; M=4.1; SD=5.1). Patients with co-morbid anxiety and depression (N=203; M=21.9, SD=11) scored significantly higher than patients with a single disorder, albeit an anxiety disorder (N= 214; M= 13.9; SD=8.7) or a depressive disorder (N= 109; M=13.3; SD=8.7). Of the anxiety disorders, patients with panic disorder and agoraphobia had the highest mean score (M=16, SD=11).We concluded that the BAI may be used as a severity indicator for anxiety disorders in primary care.

Interpretation of the main findings and comparison with the literature

In **chapter 6** the results of the above described studies are discussed. We found collaborative stepped care to be significantly more effective than care as usual. Probably the additional elements of collaborative stepped care – structured treatment steps based on cognitive behavioural therapy, active monitoring of symptoms and

follow-up, supervised care managers working in collaboration with the GP- induced this increased effectiveness. The results of our study about the effectiveness of collaborative stepped care are generally comparable to studies about collaborative care that were conducted in the United States. The effect sizes found in our study were somewhat smaller (at least in the early stages of the study), which may be explained by the gradual increase in treatment intensity that was part of our stepped care program.

Suboptimal implementation of the collaborative stepped care intervention

Contrary to our expectations, a significant proportion of patients did either not complete step 1 (22%) or did not continue to step 2 while remission was not yet achieved (18%). The fact that many patients discontinued treatment after step one may be interpreted in different ways. On the one hand, it seems favourable that these patients felt adequately equipped to cope with their anxiety after a minimal intervention. On the other hand, subclinical anxiety symptoms are an important risk factor for relapse of the anxiety disorder. Therefore, active monitoring of patients who do not reach complete remission, as was done in our intervention, is essential. Furthermore, future research may identify which patients are likely to (not) respond to guided self-help. Adherence of patients to the first step in treatment may be improved by offering a choice between initial interventions. The performance of professionals may be further increased by the implementation of a digital communication and decision support system to facilitate communication between professionals and supervision.

Methodological considerations

A strength of our study was that all professionals who participated in our study were recruited in practice settings, which enabled us to estimate the effects of collaborative stepped care as implemented in daily practice. A limitation of our study was that we had to correct for baseline differences between treatment groups in our analyses. These differences may have been caused by the design of our study (cluster randomisation). Although individual randomisation carries a risk of contamination of the effect (GPs would have to provide treatment to both intervention and control

patients) this risk may be more acceptable than the risk of baseline differences in cluster randomised trials.

Transforming primary mental health care

The studies concerning questionnaires show that questionnaires may assist in the process of diagnosing anxiety and assessing severity, in conjunct with the clinical assessment of a primary care provider. Because mental health problems are divers and prevalent in primary care, primary care personnel should ideally be provided with a mental health toolkit. This toolkit should support them to provide (preventive) intervention to patients with only symptoms, collaborative stepped care for those with a disorder and local resources for referral for patients with a severe disorder or predominantly social or relational problems.

Implications for research and practice

Future research should focus on the effectiveness of collaborative stepped care for patients with various anxiety disorders, patients with multiple (medical and mental) conditions and targeting interventions for specific patient groups. Furthermore, primary care models that integrate physical and mental health care, from prevention to chronic care need to be developed and evaluated. Financial and educational resources are necessary to facilitate implementation of collaborative stepped care in primary care in the Netherlands.

Conclusion

Collaborative stepped care is a valuable intervention that may improve the quality of primary care for anxiety disorders. Although further research is warranted, implementation of collaborative stepped care in daily practice is justified as the intervention is cost-effective compared to care as usual. Substantial efforts are needed for a widespread implementation of collaborative stepped care.

Nederlandse samenvatting

Inleiding

Angststoornissen komen veel voor

Stress, spanning en angstklachten komen veel voor. Er is sprake van een angststoornis als iemand zoveel last heeft van de angstklachten dat die hem of haar beperken in het dagelijks leven. Ongeveer één op de vijf Nederlanders krijgt eens in zijn leven een angststoornis (de Graaf *et al.* 2010). Vaak houden angstklachten lang aan, of komen in periodes terug. Dit is niet alleen nadelig voor de persoon zelf, maar ook voor de maatschappij, omdat iemand met een angststoornis zich vaker ziek meldt en meer gebruik maakt van zorgvoorzieningen.

De zorg voor mensen met een angststoornis is niet optimaal

Angststoornissen kunnen in principe goed behandeld worden met gesprekstherapie of met medicatie. Volwassenen met angstklachten komen over het algemeen eerst terecht bij hun huisarts. Hoewel de huisartspraktijk een goede plek lijkt voor de behandeling van angstklachten –laagdrempelige zorg dichtbij huis- blijkt het lastig om in de huisartspraktijk mensen met angststoornissen goed te behandelen. Hier zijn verschillende redenen voor: huisartsen zijn niet altijd voldoende ervaren in gesprekstherapie of hebben hiervoor te weinig tijd, patiënten kunnen bezwaren hebben tegen medicatie of tegen een doorverwijzing naar de psycholoog en contacten tussen hulpverleners of instellingen zijn niet altijd goed geregeld (van Marwijk 2004; Prins *et al.* 2009; Van Rijswijk *et al.* 2009; Muntingh *et al.* 2012).

Leren van de zorg voor chronische ziekten

Hoewel angststoornissen niet per definitie chronisch verlopen, bestaan de klachten vaak langdurig, of komen ze in periodes terug. Daarom is het nodig om de zorg voor patiënten met angststoornissen anders in te richten dan voor kortdurende kwalen. Voor patiënten met een angststoornis is het belangrijk dat de zorg erop gericht is hen zo goed mogelijk zelf om te leren gaan met de klachten (zelfmanagement), dat verschillende hulpverleners (zoals huisartsen en psychologen) goed met elkaar samenwerken en dat de klachten van de patiënt regelmatig worden geëvalueerd

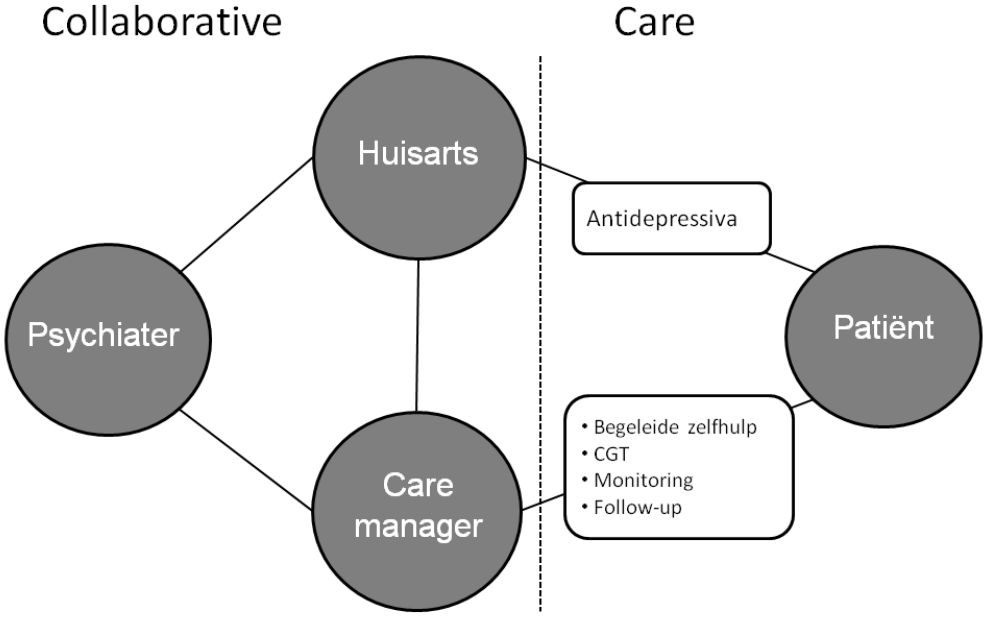
(monitoren). De huidige zorg voor patiënten met een angststoornis ziet er nog niet zo uit. We kunnen hierin leren van de zorg voor mensen met chronische aandoeningen als diabetes en hart- en vaatziekten. De zorg voor chronische ziekten wordt tegenwoordig zo georganiseerd dat de patiënt een vaste hulpverlener heeft (de praktijkondersteuner) die hem of haar ondersteunt in het omgaan met de ziekte in samenwerking met de huisarts, waarbij er vaste controlemomenten zijn en goede afspraken met andere zorgverleners. Het *collaborative care model* is een behandelmodel voor psychische stoornissen dat sterk lijkt op het hierboven beschreven model voor chronische zorg. In het collaborative care model werken verschillende hulpverleners samen (huisarts, verpleegkundige, psychiater), wordt er gewerkt met wetenschappelijk onderbouwde behandelingen, en worden de klachten van de patiënt regelmatig geëvalueerd (Katon *et al.* 2010).

Het collaborative care model

Bij collaborative care wordt de huisarts doorgaans ondersteund door een *care manager* (meestal een sociaal psychiatrisch verpleegkundige (SPV) of psycholoog), die nauw samenwerkt met de huisarts. De care manager geeft de patiënt uitleg over de klachten en de behandeling, verleent psychologische zorg met behulp van wetenschappelijk onderbouwde protocollen en evalueert de voortgang van de behandeling met de patiënt. De huisarts en care manager kunnen advies vragen aan een psychiater over de patiënt of de behandeling (Figuur 1). Collaborative care heeft goede resultaten geboekt bij de behandeling van depressie (Gilbody *et al.* 2006; Thota *et al.* 2012), met name in de Verenigde Staten, maar ook in Nederland (Huijbregts *et al.* 2012). Ook voor angststoornissen lijkt het collaborative care model veelbelovend (Smolders *et al.* 2008; Roy-Byrne *et al.* 2010), maar hier is tot nu toe nog weinig onderzoek naar gedaan.

Stepped care en collaborative care

Om de zorg betaalbaar te houden, is het belangrijk dat mensen de zorg krijgen die zij nodig hebben, maar niet meer dan dat. Hier sluit het principe *stepped care* op aan: mensen krijgen eerst een lichte vorm van zorg. Alleen als het nodig is krijgen zij een meer intensieve behandeling (Davison 2000). Hoewel dit een logisch en aantrekkelijk idee lijkt, is er nog geen sterk bewijs dat stepped care bij angststoornissen beter werkt



Figuur 1: Schematische weergave van collaborative care bij angststoornissen
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of goedkoper is dan de huidige huisartsenzorg (Bower & Gilbody 2005). Het collaborative stepped care model kan een goede methode zijn om stepped care toe te passen: met een *care manager* die de voortgang goed in de gaten houdt en een psychiater op de achtergrond die kan ingrijpen wanneer nodig.

Paniekstoornis en gegeneraliseerde angststoornis

De paniekstoornis en gegeneraliseerde angststoornis zijn twee typen angststoornissen waarvoor collaborative stepped care goed zou kunnen werken. Beide stoornissen komen regelmatig voor, mensen hebben vaak gedurende langere tijd of in periodes last van de klachten en er zijn kortdurende, wetenschappelijk onderbouwde behandelingen beschikbaar voor toepassing in de eerste lijn, die echter onvoldoende worden toegepast.

Collaborative stepped care voor huisartspatiënten met paniekstoornis en gegeneraliseerde angststoornis

Samengevat kan worden gesteld dat het *collaborative stepped care* model een veelbelovende methode lijkt om de zorg voor patiënten met een paniekstoornis of gegeneraliseerde angststoornis te verbeteren. Door het plaatsen van een *care manager* in de huisartspraktijk, die kortdurende behandelingen uitvoert, de klachten van de patiënt gedurende langere tijd in de gaten houdt en regelmatig overlegt met de huisarts en eventueel de psychiater wordt het zorgsysteem verbeterd wat tot betere behandelresultaten moet leiden. Echter, de effectiviteit van een dergelijk *collaborative stepped care* model bij paniekstoornis en gegeneraliseerde angststoornis is nog niet onderzocht. Daarom komen in dit proefschrift de volgende vraagstellingen aan de orde:

- Wat is de effectiviteit van *collaborative care* voor angststoornissen wereldwijd? (**Hoofdstuk 2**)
- Wat is de effectiviteit van *collaborative stepped care* bij patiënten met een paniekstoornis of gegeneraliseerde angststoornis in de huisartspraktijk ten opzichte van de gebruikelijke zorg? (**Hoofdstuk 3**)
- Hoe verhouden de kosten en baten van *collaborative stepped care* zich met die van de gebruikelijke zorg? (**Hoofdstuk 4**)
- Hoe kunnen vragenlijsten bijdragen aan het herkennen van een angststoornis door de huisarts en het vaststellen van de ernst van angstklachten in de eerste lijn? (**Hoofdstuk 5**)

Systematische literatuurstudie naar gerandomiseerd onderzoek over collaborative care voor angststoornissen

In **hoofdstuk 2** werd het wetenschappelijke bewijs voor de effectiviteit van collaborative care bij angststoornissen onderzocht. In wetenschappelijke databases werd gezocht naar artikelen die de resultaten beschreven van gerandomiseerde, gecontroleerde studies die een collaborative care behandeling vergeleken met een andere behandeling voor angststoornissen in de huisartspraktijk. Er werden vijf studies gevonden die aan deze criteria voldeden, met in totaal 1931 deelnemende patiënten. Vier studies waren uitgevoerd in de Verenigde Staten en één in Duitsland.

Alle studies vergeleken collaborative care met gebruikelijke huisartsenzorg. De resultaten van de vijf studies werden statistisch samengevat in een meta-analyse. Hieruit bleek dat de collaborative care interventies effectiever waren dan de gebruikelijke zorg, zeker voor patiënten met een paniekstoornis. Er werd geconcludeerd dat collaborative care waarschijnlijk een effectieve interventie is voor angststoornissen in de eerste lijn, maar dat er nog meer studies nodig zijn van buiten de Verenigde Staten en die betrekking hebben op andere angststoornissen dan de paniekstoornis.

Een Nederlands onderzoek naar de effectiviteit van collaborative stepped care bij angststoornissen

Opzet onderzoek

Hoofdstuk 3 beschrijft de opzet en resultaten van een Nederlands onderzoek naar de effectiviteit van collaborative stepped care bij angststoornissen. Aan dit cluster-gerandomiseerde, gecontroleerde onderzoek namen 43 huisartspraktijken en 31 praktijkondersteuners geestelijke gezondheidszorg (POHs-GGZ) deel. De POHs-GGZ waren allen verbonden aan één of twee huisartspraktijken. De POHs-GGZ werden via loting ingedeeld in één van twee groepen: de collaborative stepped care groep (16 POHs-GGZ) of de gebruikelijke zorg groep (15 POHs-GGZ). De POHs-GGZ en de huisartsen die in de collaborative stepped care groep werden ingedeeld, werden getraind in de collaborative stepped care interventie. Deze getrainde POHs-GGZ vervulden de functie van care manager. Er waren zes psychiaters beschikbaar die advies konden verlenen aan de care managers en de huisartsen in de collaborative stepped care groep.

Inhoud collaborative stepped care interventie

De collaborative stepped care interventie bestond uit drie stappen: 1) Begeleide zelfhulp, 2) Cognitieve gedragstherapie, 3) Medicatie (Figuur 2). De begeleide zelfhulp bestond uit een zelfhulpboek met begeleiding in vijf korte consulten door de care manager. Er stond informatie in het boek over angstklachten en er stonden oefeningen in uit de cognitieve gedragstherapie, zoals het leren herkennen van angstige gedachten en het opzoeken van moeilijke situaties (van Boeijen 2007). Stap 2

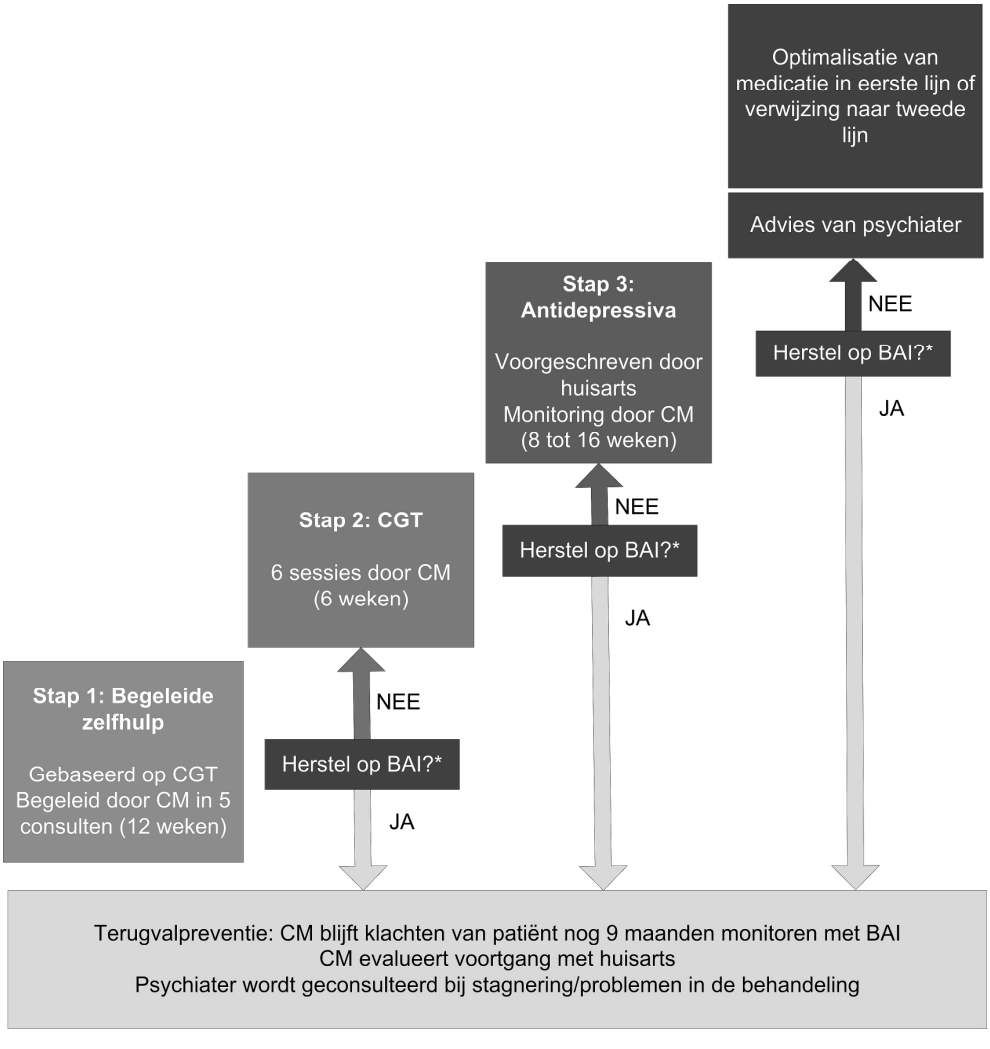
bestond uit zes sessies cognitieve gedragstherapie, gegeven door de care manager op basis van een protocol. In stap 3, medicatie, werden antidepressiva voorgeschreven door de huisarts op basis van wetenschappelijke richtlijnen. Het effect van de behandeling werd na elke stap geëvalueerd met behulp van een angstvragenlijst (de Beck Anxiety Inventory (BAI) (Beck *et al.* 1988)) door de care manager. Het doel was hierbij om een "normale" angstscore (herstel) te bereiken. Als een patiënt niet herstelde, werd de volgende stap ingezet. Was een patiënt wel hersteld, dan werd hij na de behandeling nog een aantal keer opgebeld door de care manager, om terugval in de klachten te voorkomen.

Inhoud gebruikelijke zorg

De gebruikelijke zorg verliep via de huisartsen in de gebruikelijke zorg groep. Deze huisartsen hadden alle opties tot hun beschikking die zij normaal gesproken ook hebben, zoals het zelf voeren van een aantal gesprekken, medicatie voorschrijven of verwijzen naar een eerstelijnspsycholoog of een GGZ instelling. Daarnaast konden zij patiënten verwijzen naar de POH-GGZ (die niet aanvullend getraind was).

Werven van deelnemers en analyses

Huisartsen uit beide groepen konden patiënten met een vermoedelijke angststoornis aanmelden voor het onderzoek. Daarnaast werden er patiënten geselecteerd uit het elektronisch dossier van de deelnemende huisartsen op basis van risicofactoren voor angststoornissen. Alle patiënten die aan de onderzoekscriteria voldeden en wilden meewerken aan het onderzoek kregen een diagnostisch interview om vast te stellen of er sprake was van een paniekstoornis of een gegeneraliseerde angststoornis. Uiteindelijk werden er 180 patiënten geworven voor het onderzoek: 114 in de collaborative stepped care groep en 66 in de gebruikelijke zorg groep. Deze mensen werden 12 maanden lang gevolgd en zij vulden in totaal vijf keer een vragenlijst in (om de drie maanden). Met behulp van deze vragenlijst werden onder andere de angstklachten en het zorggebruik gemeten. Statistische analyses (multilevel regressie analyses) werden gebruikt om verschillen tussen de groepen te meten.

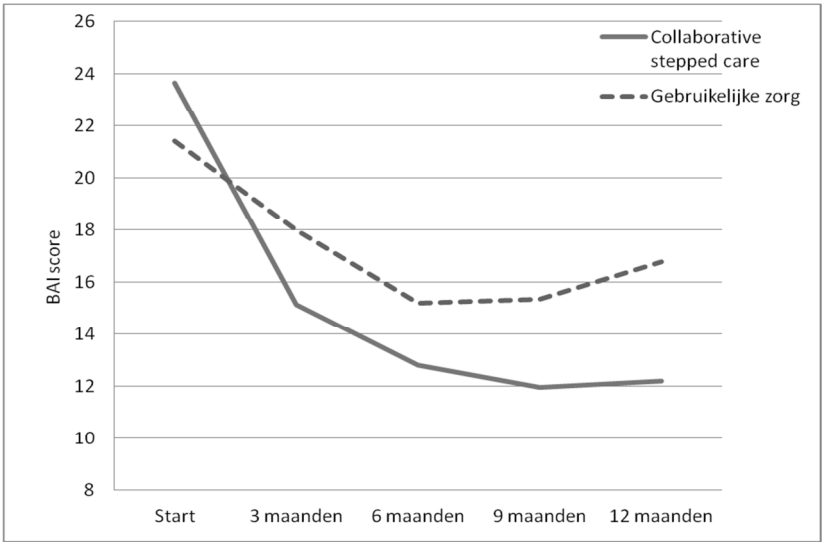


**Herstel: score op BAI vragenlijst is ≤ 11. BAI=Beck Anxiety Inventory. CM=care manager.*

Figuur 2. Het collaborative stepped care programma.

Resultaten

Zowel bij de patiënten in de collaborative stepped care groep als bij de patiënten in de gebruikelijke zorg groep namen de angstklachten af bij de vervolgmetingen (zie Figuur 3). Bij de collaborative stepped care groep was deze daling significant sterker dan in de gebruikelijke zorg groep. Daarom werd er geconcludeerd dat collaborative stepped care een effectieve methode is om patiënten met een paniekstoornis of gegeneraliseerde angststoornis te behandelen in de huisartspraktijk.



Figuur 3. Het verloop van de angstklachten (BAI score) gedurende een jaar in de collaborative stepped care groep en de gebruikelijke zorg groep.

Kosten-effectiviteit van collaborative stepped care

In een aparte analyse (**hoofdstuk 4**) werden de kosten en baten van de collaborative stepped care behandeling afgezet tegen de kosten en baten van de gebruikelijke zorg. De gemiddelde zorgkosten werden berekend per patiënt en ook de kosten die werden gemaakt door ziekteverzuim of door verminderde productiviteit werden meegenomen. De baten werden uitgedrukt als de toegenomen kwaliteit van leven bij de patiënten over een jaar gemeten. Uit deze analyse bleek dat de zorgkosten voor patiënten die de collaborative stepped care behandeling kregen gemiddeld €351,- hoger waren dan voor patiënten die de gebruikelijke zorg kregen. Echter, de kwaliteit van leven van

patiënten die de collaborative stepped care behandeling kregen nam ook sterker toe (verschil van 0,05 QALY). De kosten voor ziekteverzuim en verminderde productiviteit waren gemiddeld €955,- lager in de collaborative stepped care groep dan in de gebruikelijke zorg groep. Dit betekent dat de collaborative stepped care behandeling kosten-effectief is ten opzichte van de gebruikelijke zorg voor patiënten met een paniekstoornis of gegeneraliseerde angststoornis.

Bijdrage van vragenlijsten aan het herkennen en vaststellen van de ernst van angstklachten in de eerste lijn

In **hoofdstuk 5** worden twee studies beschreven over vragenlijsten. In de eerste studie werd onderzocht of een screeningsvragenlijst (de angstschaal van de Patient Health Questionnaire, PHQ) waarde toevoegt bij het herkennen angststoornissen bij twee patiëntgroepen: 1) huisartspatiënten die een hoog risico hebben op een angststoornis (hoog-risico patiënten) en 2) patiënten bij wie de huisarts het vermoeden heeft op een angststoornis (patiënten met een vermoedelijke angststoornis). Er namen 170 hoog-risico patiënten en 141 patiënten met een vermoedelijke angststoornis deel aan het onderzoek. Zij vulden de PHQ in en kregen een telefonisch diagnostisch interview om een angststoornis vast te stellen. Het bleek dat bij de hoog-risico patiënten het gebruik van twee screeningsvragen van de PHQ een betere voorspelling gaf dan het gebruik van de volledige PHQ. De conclusie was dat de PHQ goed gebruikt kan worden om angststoornissen op te sporen bij hoog-risico groepen en om een vermoedelijke angststoornis te bevestigen, maar dat de PHQ niet gebruikt mag worden om het bestaan van een angststoornis uit te sluiten bij patiënten bij wie de huisarts een angststoornis vermoedt. In de tweede studie uit **hoofdstuk 5** werd onderzocht of de Beck Anxiety Inventory (een korte angstvragenlijst) de ernst van de angst kon meten bij patiënten met verschillende typen angststoornissen. Er werd gebruik gemaakt van data van 1601 huisartspatiënten die deelnamen aan het NESDA onderzoek (the Netherlands Study of Depression and Anxiety). Dit cohort van huisartspatiënten bestaat uit patiënten zonder angststoornis of depressie (N=984) en patiënten met een angststoornis en/of een depressie (N=617). Bij alle patiënten werd een diagnostisch interview en de Beck Anxiety Inventory (BAI) afgenomen. De gemiddelde score op de BAI van verschillende groepen patiënten werd vergeleken: patiënten zonder

angststoornis of depressie, patiënten met één angststoornis (paniekstoornis, sociale fobie, gegeneraliseerde angststoornis of agorafobie), patiënten met meerdere angststoornissen, patiënten met een depressie en patiënten met een angststoornis en een depressie. De patiënten met een angststoornis scoorden gemiddeld hoger dan patiënten zonder een angststoornis of depressie, waarbij de patiënten met een paniekstoornis met agorafobie het hoogst scoorden. Patiënten met meerdere angststoornissen scoorden weer hoger dan patiënten met één angststoornis. Opvallend was dat er geen verschil werd gevonden in gemiddelde score tussen patiënten met een depressie en patiënten met een angststoornis. Er werd geconcludeerd dat de BAI goed gebruikt kan worden om de ernst van de angst te meten bij huisartspatiënten met verschillende typen angststoornissen, maar dat de score op de BAI geen onderscheid maakt tussen een angststoornis of een depressie.

Discussie

In de discussie (**Hoofdstuk 6**) worden de resultaten van de verschillende studies en de aanbevelingen voor praktijk, beleid en onderzoek besproken.

De kosten- effectiviteit van collaborative stepped care

Uit **Hoofdstuk 3** bleek dat collaborative stepped care een effectieve behandeling is ten opzichte van de gebruikelijke zorg. De toegevoegde elementen van collaborative stepped care – gestructureerde behandelstappen gebaseerd op cognitieve gedragstherapie, het actief monitoren van klachten en terugvalpreventie, care managers die supervisie kregen en samenwerkten met de huisarts –hebben waarschijnlijk bijgedragen aan deze hogere effectiviteit. Dit resultaat komt redelijk overeen met de resultaten van Amerikaans onderzoek naar de effectiviteit van collaborative care (Roy-Byrne *et al.* 2001; Roy-Byrne *et al.* 2005; Rollman *et al.* 2005; Roy-Byrne *et al.* 2010). De Amerikaanse studies vonden echter een groter effect van de collaborative care behandeling dan wij in onze studie gedurende de eerste 9 maanden. Een belangrijke verklaring hiervoor lijkt te zijn dat onze stepped care behandeling in het begin minder intensief was dan de combinatie van medicijnen en cognitieve gedragstherapie die meestal werd ingezet in de Amerikaanse studies. In vergelijking met een Nederlandse stepped care studie (Seekles *et al.* 2011) vonden wij juist een groter effect, wat

verklaard zou kunnen worden door de grotere rol van de *care manager* en de samenwerking met de huisarts en psychiater in ons onderzoek. De hogere zorgkosten van de collaborative stepped care behandeling vergeleken met de gebruikelijke zorg werden voor het grootste deel verklaard door de inzet van de care manager. De extra zorgkosten van de collaboratie stepped care interventie werden echter op andere gebieden (gezondheid en arbeidsproductiviteit) "terugverdiend".

Sterke en zwakke punten van het onderzoek

Een sterk punt van het effectonderzoek (hoofdstuk 3) is dat de behandeling werd uitgevoerd door professionals die in de praktijk werken, waardoor de resultaten de dagelijkse praktijk goed benaderen. Daarnaast werden er statistische analyses gebruikt die geschikt zijn voor het analyseren van groepen (multilevel analyse). Er zijn ook een aantal beperkingen van het onderzoek te noemen. Wij hebben in dit onderzoek gekozen voor cluster randomisatie: POHs-GGZ en hun huisartspraktijken werden ingedeeld in een interventie- en een controlegroep. Dit is gedaan om de interventies strikt gescheiden te houden: de zorgverleners in de interventiegroep gaven de collaborative stepped care interventie en de hulpverleners in de controlegroep verleenden de gebruikelijke zorg. Echter, het probleem ontstond dat huisartsen in de interventiegroep meer patiënten aanmeldden voor de studie dan de huisartsen in de controlegroep. Huisartsen in de controlegroep waren wellicht minder gemotiveerd om patiënten aan te melden voor de studie omdat zij hun patiënten niets "nieuws" konden bieden. Daarentegen hadden huisartsen in de interventiegroep wellicht een verhoogde aandacht voor patiënten met angststoornissen door het werken met de nieuwe methode. Behalve dat er meer patiënten deelnamen aan de interventiegroep bleken er ook inhoudelijk verschillen te bestaan tussen patiënten in de interventie- en controlegroep bij de start van het onderzoek (baselinemeting). Voor deze verschillen is gecorrigeerd in de analyses. Echter, voor vervolgonderzoek is het wellicht beter om de patiënten in plaats van de hulpverleners random toe te wijzen aan een interventie.

Verbeteren van de collaborative stepped care interventie

Hoewel de collaborative stepped care interventie goed resultaat had, werkte het niet voor alle patiënten even goed. Een deel van de patiënten maakte ofwel de eerste stap

van de behandeling (begeleide zelfhulp) niet af (22%) of ging niet door met de tweede stap terwijl ze nog niet volledig hersteld waren van de angststoornis (18%). Dat veel mensen van verdere behandeling afzagen na stap 1 kan worden gezien als een goed resultaat: veel mensen gaven aan voldoende handvatten te hebben om verder te kunnen. Echter, uit onderzoek weten we dat onvolledig herstel een hoger risico geeft op terugval in de angstklachten. Het is daarom belangrijk om de deze patiënten goed in de gaten te blijven houden en een andere interventie aan te bieden wanneer nodig. De betrokkenheid van patiënten bij de behandeling zou verder verhoogd kunnen worden door hen een keuze tussen behandelingen aan te bieden in plaats van een vast behandelprogramma. Vervolgonderzoek zou inzicht kunnen geven in welke patiënten voldoende baat hebben bij begeleide zelfhulp en welke niet. Een andere mogelijke verbetering is het gebruik van een digitaal communicatie systeem inclusief gedeeld patiëntendossier om de samenwerking tussen professionals (en daarmee de kwaliteit van zorg) nog verder te verhogen.

Gebruik van vragenlijsten voor het opsporen van angststoornissen en het vaststellen van de ernst van de angst

Voor het aanbieden van collaborative stepped care is het eerst nodig dat er een diagnose van een paniekstoornis of gegeneraliseerde angststoornis wordt gesteld. Daarom is in hoofdstuk 5 onderzocht of vragenlijsten een goede toevoeging kunnen zijn aan het diagnostisch proces in de huisartspraktijk. Het gebruik van vragenlijsten wordt aanbevolen, maar altijd als onderdeel van een gesprek met de patiënt. Er moeten nog strategieën worden gevonden die ervoor zorgen dat huisartsen die het lastig vinden om angststoornissen op te sporen hierbij te ondersteunen. Selectieve screening van hoog-risicopatiënten kan hierbij een optie zijn, maar alleen als de huisartspraktijk beschikking heeft over laagdrempelige behandelingen, zoals begeleide zelfhulp of internetinterventies.

Aanbevelingen voor onderzoek

Het is belangrijk om te onderzoeken of collaborative stepped care ook kosten-effectief is voor patiënten met andere angststoornissen, zoals sociale fobie. Daarnaast moet er onderzocht worden hoe de zorg voor patiënten die meerdere aandoeningen

tegelijkertijd hebben (co- of multimorbiditeit) het beste ingericht kan worden. Uiteindelijk is er een geïntegreerd pakket nodig aan interventies, *tools* (zoals vragenlijsten) en samenwerkingsverbanden die huisartsen kunnen gebruiken om de vraag naar hulp bij psychische klachten goed op te kunnen vangen.

Aanbevelingen voor praktijk en beleid

Collaborative stepped care zal niet vanzelf zijn weg vinden naar de huisartspraktijk. Hier is niet alleen scholing van huisartsen en *care managers* voor nodig, maar ook financiële en praktische ondersteuning. Een belangrijke stap in de goede richting is dat de praktijkondersteuner huisarts GGZ (POH-GGZ) een grotere rol krijgt in de eerstelijnszorg omdat deze professional de rol van *care manager* op zich kan nemen. Daarnaast zou het goed zijn als psychiaters en andere professionals op basis van een consulttarief advies konden bieden aan eerstelijns hulpverleners en als er geld beschikbaar komt voor de implementatie van collaborative stepped care.

Conclusie

Collaborative stepped care is een veelbelovende, kosten-effectieve interventie voor de behandeling van angststoornissen in de huisartspraktijk. Vervolgonderzoek is wenselijk, maar op basis van dit proefschrift kan gesteld worden dat collaborative stepped care het waard is om brede toepassing te vinden in de Nederlandse huisartspraktijk.

REFERENCES

Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* **56**, 893-897.

Bower, P. & Gilbody, S. (2005). Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry* **186**, 11-17.

Davison, G. C. (2000). Stepped care: doing more with less? *Journal of Clinical Psychology* **68**, 580-585.

de Graaf, R., ten Have, M., & van Dorsselaer, S. (2010). De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: Opzet en eerste resultaten [Mental health in the Dutch general population. Design and results of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) In Dutch.].

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern.Med* **166**, 2314-2321.

Huijbregts, K. M., de Jong, F. J., van Marwijk, H. W., Beekman, A. T., Ader, H. J., Hakkaart-van, R. L., Unutzer, J. & van der Feltz-Cornelis CM (2012). A target-driven collaborative care model for Major Depressive Disorder is effective in primary care in the Netherlands. A randomized clinical trial from the depression initiative. *J Affect Disord.*

Katon, W., Unutzer, J., Wells, K. & Jones, L. (2010). Collaborative depression care: history, evolution and ways to enhance dissemination and sustainability. *Gen.Hosp.Psychiatry* **32**, 456-464.

Muntingh, A. D. T., Hermens, M., Franx, G., Van Splunteren, P., & Nuyen, J. (2012). Hoe verhouden de werkelijke en wenselijke eerstelijns depressiezorg zich tot elkaar? Resultaten van een verkennend onderzoek in de huisartspraktijk.*Trendrapportage GGZ. Deel 3: Kwaliteit en effectiviteit.* (ed. J. Nuyen). Trimbos-instituut: Utrecht.

Prins, M. A., Verhaak, P. F., Van der Meer, K., Penninx, B. W. & Bensing, J. M. (2009). Primary care patients with anxiety and depression: need for care from the patient's perspective. *J Affect Disord* **119**, 163-171.

Rollman, B. L., Belnap, B. H., Mazumdar, S., Houck, P. R., Zhu, F., Gardner, W., Reynolds, C. F., III, Schulberg, H. C. & Shear, M. K. (2005). A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. *Arch Gen Psychiatry* **62**, 1332-1341.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J., Bystritsky, A., Welch, S. S., Chavira, D. A., Golinelli, D., Campbell-Sills, L., Sherbourne, C. D. & Stein, M. B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *Journal of the American Medical Association* **303**, 1921-1928.

Roy-Byrne, P. P., Craske, M. G., Stein, M. B., Sullivan, G., Bystritsky, A., Katon, W., Golinelli, D. & Sherbourne, C. D. (2005). A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* **62**, 290-298.

Roy-Byrne, P. P., Katon, W., Cowley, D. S. & Russo, J. (2001). A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* **58**, 869-876.

Seekles, W., van Straten, A., Beekman, A., van Marwijk, H. & Cuijpers, P. (2011). Stepped care treatment for depression and anxiety in primary care. a randomized controlled trial. *Trials* **12**, 171.

Smolders, M., Laurant, M., Roberge, P., Van Balkom, A., Van Rijswijk, E., Bower, P. & Grol, R. (2008). Knowledge transfer and improvement of primary and ambulatory care for patients with anxiety. *Can J Psychiatry* **53**, 277-293.

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease, D. E., Jr. & Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med* **42**, 525-538.

van Boeijen, C. A. Handboek Begeleide Zelfhulp: Overwinnen van angstklachten *(Handbook guided self help: Overcoming anxiety).* 2007. Apeldoorn.

van Marwijk, H. (2004). How to improve mental health competency in general practice training?--a SWOT analysis. *Eur J Gen Pract* **10**, 61-65.

Van Rijswijk, E., van Hout, H., van de Lisdonk, E., Zitman, F. & Van Weel C. (2009). Barriers in recognising, diagnosing and managing depressive and anxiety disorders as experienced by Family Physicians; a focus group study. *BMC Fam Pract* **10**, 52.

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Curriculum Vitae

1983	Born in Berkel en Rodenrijs
1996-2002	Pre-university education, Dalton, Voorburg
2002-2006	Bachelors degree Psychology, Utrecht University
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2008-2013	PhD student at Trimbos institute and Tilburg University
2010	Summer school "Health care and Social Systems", Alpbach, Austria (grant)
2011	Working visit to Johns Hopkins University (Baltimore) and University of Washington (Seattle), Travelgrant EMGO+
2008-present	Research associate at Trimbos-institute
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Publications

Muntingh, A.D.T., van der Feltz-Cornelis, C.M., van Marwijk, H.W.J., Spinhoven, Ph., Assendelft, W.J.J., de Waal, M.W., Hakkaart-van Roijen, L. Adèr, H.J. & van Balkom, A.J.L.M. (2009). Collaborative stepped care for anxiety disorders in primary care: aims and design of a randomized controlled trial. Biomed Central Health Services Research, 9, 1, 159.

Muntingh, A. (2010). Collaborative stepped care. De nieuwe weg vooruit bij de behandeling van angststoornissen in de eerste lijn? [Collaborative stepped care. The way forward for treating anxiety disorders in Dutch primary care?] Silhouet, 3, p. 34-35.

Meeuwissen, J., Sinnema, H. & Muntingh, A. (2011). Organisatie van zorg. In: Handboek angststoornissen, van Balkom, A., Oosterbaan, D., Visser, S. & van Vliet, I. (red.). [Organisation of care. In: Handbook of anxiety disorders. In Dutch.]. Utrecht: De Tijdstroom.

Muntingh, A. D. T., van der Feltz-Cornelis CM, Van Marwijk, H. W. J., Spinhoven, A.J.L.M. van Balkom, B. Penninx. (2011). Is the Beck Anxiety Inventory a good tool to assess the severity of anxiety? A primary care study in the Netherlands Study of Depression and Anxiety. Biomed Central Family Practice, 12: 66.

Muntingh, A. D. T., Hermens, M., Franx, G., Van Splunteren, P., & Nuyen, J. (2012). Hoe verhouden de werkelijke en wenselijke eerstelijns depressiezorg zich tot elkaar? Resultaten van een verkennend onderzoek in de huisartspraktijk. [How does the actual depression care relate to optimal depression care? Results of an exploratory study in Dutch primary care. In Dutch]. In *Trendrapportage GGZ. Deel 3: Kwaliteit en effectiviteit.* (ed. J. Nuyen). Trimbos-instituut: Utrecht.

Sinnema, H. Muntingh, A. & Van Marwijk, H. (2012). De eerstelijnszorg in beweging. Maandblad Geestelijke Volksgezondheid, 67, 1/1, p. 2-12.